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A STATISTICAL STUDY OF SIX HUNDRED AND SEVENTY-ONE CASES OF APPENDICEAL PERITONITIS* (Concluded)

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PART II. TWO HUNDRED AND TWENTY-SEVEN CASES WITH PALPABLE MASS ON ADMISSION TO THE HOSPITAL

IN the previous section, dealing with appendiceal peritonitis unassociated with a demonstrable mass, we pointed out the fallacy of attempting a classification on a purely pathological basis, and again we should like to state that it is only by implication or an unjustifiable exhaustive exploration that such a distinction can be made.

The presence of a palpable mass is of major importance in determining the course of treatment and in influencing the prognosis. It is indisputable evidence of a variable degree of localization of the inflammatory process and hence serves to establish a very different clinical entity from those cases in which the possibility of the formation of such a mass is still problematical, and in which it is unjustifiable to assume that such localization will of necessity ever take place.

We have used the term "mass" advisedly throughout this study because a palpable inflammatory tumor is not necessarily synonymous with an "abscess" within the usual meaning of the word. Much confusion has arisen because of the ill-defined usage of the term "appendiceal abscess," which has been employed in certain cases to describe an extensive area of inflammatory fixation about a gangrenous appendix, and in others, a small collection of pus with a negligible number of surrounding adhesions. The term "mass" refers to a tumor of inflammatory origin, of sufficient size to be demonstrated by palpation; only secondary significance is attached to the fact that such a mass might be constituted in part of a variable amount of frank pus.

The palpation of a mass in the course of physical examination was possible in 154, or 68 per cent, of these 227 cases. In 32, or 14 per cent, the mass was first noted after the administration of an anesthetic, but before the incision had been made. In 32, or 14 per cent, no mass was noted prior to opening of the peritoneal cavity, but at exploration an inflammatory tumor was found that, from its size and location, should presumably have been detected. In the remaining 9 (4 per cent) cases, not only was the mass not felt preoperatively, but even with the abdomen opened, it seemed unreasonable to suppose from its relative inaccessibility to external or rectal palpation that it could have been discovered prior to operation.

From this, it can be seen that in 82 per cent of these cases the preoperative decision concerning the type of treatment the patient was to receive should have taken into consideration the fact that a mass was present as unmistakable evidence that localization of the infectious process had occurred. It is clear that in many cases the surgeon failed to palpate the abdomen after relaxation had been secured, and before making his incision, and thus embarked on a course of treatment founded on an erroneous conception of the lesion present. It is our opinion that in cases in which a definite mass is first detected after the patient is anesthetized, the question of proceeding with the operation at that time in the light of this new finding should be re-evaluated, for the danger of premature disrup-

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tion of a definite but inadequately established walling-off process may far outweigh the danger of a second anesthetic.

In a study that professes to be concerned with the clinical problems presented by patients suffering from appendicitis with an associated mass, it may seem illogical to include the 18 per cent of cases in which the true nature of the lesion was not appreciated before the peritoneal cavity was opened. We believe that the inclusion of these cases is not inconsistent with our conception that the clinical problem of appendiceal peritonitis with mass formation is fundamentally different from that in which no such walling off has taken place, and that these cases differ only in the stage of investigation at which the true status of the disease was appreciated.

The number of patients with appendiceal peritonitis and a mass who were admitted to the hospital annually from 1929 to 1940 has changed but little, and the proportion considered "very ill" on admission has remained relatively constant (Table 1). The annual number of all patients admitted to the Massachusetts General Hospital with a diagnosis of acute appendicitis has remained essentially the same. Since there has been a yearly constancy in the number of patients with appendiceal peritonitis in any form, it appears that the incidence of cases that have been permitted to progress to perforation before being referred to the hospital has shown no definite tendency to decrease.

TABLE 1. *Comparative Incidence of Appendiceal Peritonitis with Mass, together with Proportions and Mortality Rates of the Very Ill Patients.*

YEAR	NO. OF CASES	APPENDICEAL PERITONITIS WITH MASS	VERY ILL PATIENTS ON ENTRY	
			INCIDENCE	MORTALITY
		%	%	%
1929–1930*	33	7	3	0
1931–1933	69	11	12	25
1934–1936	60	9	22	15
1937–1939	65	10	15	20
Total	227			
Averages		9.4	14	19

*It should be noted that this tabulation covers only two years instead of the three-year tabulation of the subsequent periods.

The well-recognized fact that there is a higher incidence of uncomplicated appendicitis in males than in females was likewise true in the cases of appendiceal peritonitis with an associated mass. Almost two thirds (64 per cent) of these cases occurred in males, and this figure so closely approximates the sex ratio (63 per cent males) in our study of cases without palpable mass that one may infer that if acute appendicitis goes on to peritonitis, the sex of the patient is no guide to whether or not clinically demonstrable localization will take place. The mortality in this series was strikingly higher in males (9.0 per cent) than in females (3.7 per cent), whereas the reverse was true in the cases in which no mass was present.

The well-recognized higher mortality rate in the extremes of life in appendicitis of all types is seen to be especially striking when only patients with appendiceal peritonitis and palpable mass formation are considered (Table 2). Although nearly half (46 per cent) these cases occurred between the ages of fifteen and fifty years, there was but a single death in this group, whereas in patients under fifteen there was a mortality of 9.6 per cent, and over the age of fifty it reached 16 per cent.

TABLE 2. *Age Incidence and Mortality.*

AGE	NO. OF CASES	AGE INCIDENCE	NO. OF DEATHS	MORTALITY
yr.		%		%
1-15	73	32	7	10
16-50	104	46	1	1
51 and over	50	22	8	16
Totals	227		16	
Average				7.0

PROGNOSTIC SIGNIFICANCE OF HISTORY

Duration of Illness Before Operation

Operation carried out promptly after the onset of acute appendicitis is attended with a rapid recovery of the patient and a negligible mortality. When symptoms of the disease have been present for over twenty-four hours, the inflammation may either subside spontaneously or progress to involve the peritoneal cavity, and there are no infallible criteria for judging which of these eventualities will take place. The duration of the disease as a factor in the clinical prognosis is of greatest consequence during this indeterminate stage, when the exact nature of the lesion present is largely a matter of conjecture. However, the presence of a mass in the region of the appendix is indisputable evidence of at least a partially successful localization of the inflammation to that area, and the value of our figures regarding the duration of the disease in this series of cases consists largely in providing data from which one can decide when in the course of the condition such a mass can surgically be approached most safely. In certain cases, especially in the very young and the elderly patients, a brief history was suggestive of inaccuracies concerning the recorded time interval of the disease, for a demonstrable inflammatory mass rarely becomes established within forty-eight hours.

To illustrate a significant number of cases for each comparative period, the figures shown in Table 3 have been tabulated at intervals of forty-eight hours. It is apparent, from our experience

in 56 cases, that operation for appendicitis with an associated mass within the first four days of the disease is attended with a low mortality (3.1 per cent). This is in striking contrast to our findings of a 12.5 per cent mortality in patients with ruptured appendix without mass formation operated on within this same period, and emphasizes more dramatically than any of our other comparative figures the fundamental clinical difference between these two groups.

During this relatively early stage of the disease, the mass usually consisted of thickened omentum wrapped about the appendix, with little or no frank pus. This effective localization of the process, in a form that did not predispose to the spread of infection at the time of operation and made possible an unerring approach through the most favorable incision, provided the chief factor in the low mortality of this group.

In the forty-eight-hour period of the fifth and sixth days of the disease, there was an abrupt and startling rise in the death rate—to 17.4 per cent. From the sixth to the twelfth day of the disease, there was a definite but not unbroken trend toward a lower mortality rate, and after this period the mortality reached essentially the same figure (3.2 per cent) that had obtained in the first four days of the disease.

TABLE 3. *Incidence and Mortality According to Duration of Disease before Operation.*

Duration of Disease at Time of Operation	No. of Patients	Incidence	Mortality
days		%	%
1 and 2	18	8	6
3 and 4	38	17	3
5 and 6	23	11	17
7 and 8	38	17	8
9 and 10	24	11	4
11 and 12	18	8	17
13 and over	63	28	3
Total	222*		
Average			6.7

*Four nonfatal cases and 1 fatal case were treated without operation.

It is therefore apparent that when a mass is present, operation done on or before the fourth or after the twelfth day is a relatively safe procedure, with but a 3 per cent mortality. Surgery carried out on the fifth, sixth or seventh day of the illness, however, is especially hazardous, accounting for nearly half (7) the deaths, although only one fifth (21 per cent) of the patients were operated on at that time.

Chills

In 18, or 8 per cent, of the cases, there was a definite history of chills during the preoperative course of the disease. There was no mortality in this group of patients, and although the number is small, it suggests that the occurrence of chills during the onset of acute appendicitis that goes on to form an inflammatory mass has little prognostic significance. Furthermore, a comparison of this with our other series of cases, in which the incidence of chills was essentially the same (9 per cent), leads us to believe that the occurrence of chills preoperatively is of essentially no help in determining the likelihood that the inflammatory process will extend, in contrast with its manifestation of the signs of localization.

In 1 case, in which incision and drainage without appendectomy were carried out on the twelfth day of the disease, the patient suffered chills postoperatively. The patient ran a septic course following operation and finally died, sixty-two days after drainage, of multiple liver abscesses and pylephlebitis, confirmed by autopsy.

Previous Attacks

One quarter (26 per cent) of the patients gave a history of one or more previous attacks, with a mortality somewhat higher for this group (8.3 per cent) than for the cases in which there was no note of an earlier attack (5.9 per cent). It would be misleading to try to draw conclusions from this relatively small difference in mortality rates, but it is of some interest that in the cases of appendiceal peritonitis without mass the apparent influence of previous attacks was favorable rather than unfavorable and that the incidence of cases in which a history of such attacks was recorded was definitely higher (40 per cent).

Other Factors

In the first series of cases, we showed that when appendiceal peritonitis occurred and no subsequent mass developed, 25 per cent of the histories revealed a sudden episode of increased pain that was interpreted as marking the time of perforation and was of helpful prognostic significance. Only 15 per cent of the cases with a mass, however, gave any clue to when perforation might have taken place, and this fact, when available, was primarily of academic interest, for in all these cases, by the time the patient reached the hospital, localization was an accomplished fact.

A study of the patient's bowel habits immediately preceding and following the onset of symptoms did not bring out any trend of diagnostic or prognostic value. In 22 per cent of the histories, there was some definite note of cathartics, and in these cases the mortality rate (10 per cent) was twice that of the remaining cases (5.6 per cent), in which either no laxatives were mentioned or the specific avoidance of their use was so stated.

Prognostic Significance of Physical Examination

Degree of Illness

It has been routine in our hospital records to enter on the physical sheet the examiner's impression of whether the patient was "very ill," "moderately ill" or "not ill." The distinction between the last two groups was so poorly defined in many cases that the patients were grouped together under the single heading of "not very ill." This note is based primarily on the surgeon's intuitive evaluation of the patient's appearance, and it is interesting that in these cases, as well as in those without mass formation, it is the most significant of all the preoperative data.

Table 1 shows that 14 per cent of the patients were very ill on admission, with a mortality rate nearly four times as high (19 per cent) as that for those who were not considered very ill (5 per cent). Well over a third (42 per cent) of the very ill survivors ran stormy convalescences, as contrasted with only one quarter (25 per cent) of the remaining patients. Taken in conjunction with our first series, it is seen that very ill patients were over twice as common (32 per cent) and showed nearly twice the mortality rate (34 per cent) when no mass was present as when a mass existed.

The incidence of very ill children fifteen years or under (25 per cent) was over twice as great as that for patients between the ages of fifteen and fifty (8 per cent), or over that age (12 per cent). This explains in part the high mortality in children, but cannot be advanced as the cause of the even higher rate found in the elderly group.

Stage of Treatment at Which Mass was Detected

In the 68 per cent of the cases in which the presence of the mass was appreciated before operation and before an anesthetic was administered, the mortality (Table 4) was less than half (5 per cent) that found in the remaining cases (12 per cent). Undoubtedly, the fact that it was possible to palpate without anesthesia an inflammatory tumor in 154 cases means that in this group the process had become better established or was more favorably located in the right gutter than in the other cases. One would expect the preoperative history to be longer when a mass could be made out on physical examination, and this was borne out by the facts.

Table 4. *Incidence and Mortality on Basis of When Mass Was Detected.*

Mass Detected	No. of Cases	Incidence %	No. of Deaths	Mortality %
On physical examination	154	68	7	5
Under anesthesia	32	14	4	13
At operation (should have been felt preoperatively)	31	14	4	13
At operation (could not have been felt preoperatively)	10	4	1	10
Totals	227		16	

In the 14 per cent of the cases in which a mass was first felt under anesthesia, the mortality was 13 per cent. In no case did a surgeon who discovered a mass on the operating table desist from proceeding with surgery, although such a policy has been successfully adopted subsequent to the period covered in this report.

In all the remaining cases (18 per cent), in which the mass was discovered only after the peritoneal cavity had been opened, appendectomy or drainage was carried out at that time with a mortality of 12 per cent. In only 2 such cases did the operator close his original incision and drain the area through a lateral approach; these patients made an uneventful recovery, and we are confident that many of the others would have fared better had similar mental flexibility been shown more frequently.

So far as could be determined from the records, the majority of the masses were located laterally, and detection of the mass and ease of drainage without contamination of the general peritoneal cavity were naturally greatly facilitated.

Absent Peristalsis

The fact that the infection had progressed to the point where localization was demonstrable as an inflammatory mass suggests that the greater part of the general peritoneal cavity was free of active infection at the time of admission. This relative freedom from widespread infection is confirmed by the fact that in 122 cases peristalsis was stated as being normal in 83 per cent, as contrasted with 26 per cent of the cases without a mass. Whereas, in the latter cases, absence of peristalsis was attended with a mortality of 28 per cent and provided one of the most significant and unfavorable physical signs, in this series of cases it was of little prognostic advantage.

Prognostic Significance of Laboratory Data

The average white-cell count for all patients in this series was 22,000, with a high percentage of polymorphonuclear cells in the relatively small number of cases in which differential counts were done. The pulse rate averaged 114 in the very ill patients and 106 in those who were not very ill. In no case was the admission temperature over 103.5°F., and in nearly one third (30 per cent) it was under 100°F. by mouth. These facts served merely to confirm the preoperative clinical diagnosis, and the prognostic significance of the leukocyte-pulse ratio, on which we laid great

emphasis when considering the patients without mass formation, is meaningless in this series.

Prognostic Significance of Diagnostic Errors

The diagnosis in many of the cases in which the mass was not detected preoperatively was "acute appendicitis," and strictly speaking might be considered mistaken. In an indeterminate number of cases, a diagnosis of "appendiceal abscess" was made in which no appendicitis was found, and 1 such patient, in whom the diagnosis was persisted in postoperatively, died of unsuspected carcinoma of the cecum three months following discharge.

Exclusive of these errors, a mistaken diagnosis was made in nearly one tenth (9 per cent) of the cases in this series. Nearly half these (10 cases) were erroneously diagnosed as either benign (3 of ovary) or malignant (2 of cecum, 1 of colon, 1 of kidney, 1 retroperitoneal and 2 unclassified) neoplasms. With these 10 cases, as with 4 others (3 of hernia and 1 of cirrhosis and ascites), it was primarily a misconception of the nature of the mass that was the confusing factor in diagnosis. In 2 of these, the diagnosis of malignant tumor was persisted in even after the peritoneal cavity had been opened, and in both an ileotransverse colostomy was carried out as the initial step of a two-stage procedure. All the patients survived following removal of the appendix (12 cases) or drainage alone (2 cases).

In the remaining 7 cases (3 of pelvic inflammation, 2 of cholecystitis, 1 of enteritis and 1 of nephritis), a misinterpretation of the manifestations of infection gave rise to the diagnostic error. One of these patients died following surgery on the gall bladder, and a second death occurred in a patient with renal infection and diabetes who was moribund on entry and was not considered to have any surgical lesion but in whom an unsuspected appendiceal abscess was discovered at autopsy three days after admission. The other 5 patients all lived following appendectomy (3 cases), drainage (1 case) or spontaneous subsidence of the process without surgery (1 case).

Because of the possibility of revising with relative safety the original intent of the operation after the peritoneal cavity had been opened and the true nature of the lesion determined, the mortality rate for all the above cases (9.5 per cent) was only slightly higher than that in those correctly diagnosed preoperatively (6.8 per cent). This is in striking contrast to the situation found in the cases of appendiceal peritonitis without mass formation, in which an incorrect preoperative diagnosis frequently resulted in treatment that was incompatible with recovery.

Summary of Prognostic Preoperative Factors

In the patients without a mass, we attempted to estimate the relative prognostic value of certain preoperative findings by citing the contrasting mortality rates occasioned by the presence or absence of a given factor. The same procedure has been followed in Table 5 for this series of cases in which the appendiceal peritonitis was associated with a mass. Again, it should be pointed out that this evaluation attempts merely to approximate the true prognostic significance of each factor, for these were found in such varying combinations that the accuracy of their isolated ratings can be only relative.

Table 5. *Relative Prognostic Value of Various Clinical Factors, as Determined by the Mortality Rate Associated with Each Factor, Based on 227 Cases with a Total Mortality of 7.0 Per Cent.*

Clinical Factor*	Mortality with Factor Present	Mortality with Factor Absent
	%	%
Patient very ill on admission	19	5
Patient under fifteen or over fifty years	12	1
Operation on fifth, sixth or seventh day of disease	15	5
Mass not detected on physical examination	12	5
Males	9	4
Cathartics given preoperatively	10	6
Mistaken preoperative diagnosis	10	7

*In 18 cases with preoperative chills, there were no deaths, but this number is too small to have statistical value.

Influence of Treatment on Mortality Rate

Choice of Treatment

No operation. In 5 cases, no operation was carried out during the initial hospital admission. In 2 of these, the reason for withholding surgery was a mistaken diagnosis. One was the patient with an original diagnosis of pelvic inflammatory disease who gave increasingly convincing evidence during her hospital stay that the inflammatory mass that gradually subsided without operation was probably of appendiceal origin, and the other was the patient with renal damage who died three days after entry.

Of the 3 unoperated cases correctly diagnosed as appendiceal abscess, the infection in 1 was satisfactorily handled by spontaneous drainage into the rectum. Another patient was discharged against advice, only to be readmitted for an uneventful incision and drainage and subsequent appendectomy; and the third patient, a nine-year-old child whose mass subsided during a hospital stay of seventeen days, returned three weeks later with a recurrence of symptoms that necessitated appendectomy with drainage. The fact that so few pa-

tients were treated without operation lessens the value of the statistical mortality of 20 per cent for this form of treatment.

Because in this series there was only 1 case in which an inflammatory mass subsided without operation, spontaneous drainage or death, we believe that it must be extremely rare in an unoperated case for a localized mass secondary to a ruptured appendix to subside completely without drainage. The persistence of the inciting cause of the infection undoubtedly best explains why conservative treatment is so rarely effective. This is in contrast to the course of an inflammatory mass that develops following appendectomy, for such a process subsided without operation in half those cases in both this and our earlier series in which it was present during the convalescence.

Immediate operation. Since a mass was present in all these patients, the first consideration was when surgical attack could most safely be carried out. The urgency of operation found in many of our cases of ruptured appendix without associated masses was not a factor in this series in which the danger of spontaneous spread could be assumed to be practically nonexistent. Every patient about to undergo surgery should receive appropriate preoperative measures to combat existing dehydration, and for that reason we allowed an arbitrary time limit of six hours to carry out such measures; within this period, we still considered that operation was done "immediately." Delay beyond that period in this series of cases implies that we believed that the local process would progress to a stage more favorable to surgery if such delay was instituted.

TABLE 6. *Comparative Incidence of Immediate and Deferred Operation and the Operative Mortality of Immediate Operation.*

PERIOD	NO. OF CASES OF IMMEDIATE OPERATION	NO. OF CASES OF DEFERRED OPERATION	INCIDENCE OF IMMEDIATE OPERATION	OPERATIVE MORTALITY OF IMMEDIATE OPERATION
			%	%
1929–1930*	26	7	79	12
1931–1933	56	13	81	7
1934–1936	32	25	56	7
1937–1939	29	34	46	3†
Totals	143	79		
Averages			64	6.7

*Note that this tabulation covers only two years instead of the three-year tabulation of the subsequent periods.

†There have been no deaths in the last 44 consecutive cases.

Whereas during the first five years of this series, four fifths (80 per cent) of the patients were operated on soon after entry (Table 6), this has been true in slightly less than half (49 per cent) the cases during the last five years. This striking change in policy undoubtedly constitutes one of the factors responsible for the downward trend of the mortality from 12 per cent in the earlier years to 3 per cent more recently.

In 143 cases, immediate operation was carried out, with a mortality of 7 per cent and an uneventful convalescence in 73 per cent of the survivors. In the cases with a history of four days or less operated on within six hours of entry, the mortality was 4 per cent, whereas during the fifth, sixth and seventh days of the disease, there was a mortality of 12 per cent in the cases treated by immediate surgery. Following the seventh day, immediate operation was attended with a 7 per cent mortality.

During the first four days of the disease, immediate operation was carried out more than ten times as often as deferred treatment, and during the fifth, sixth and seventh days, despite a mortality of 11.7 per cent, immediate operation was adopted three times as frequently as conservative observation. Later than the seventh day, the mortality for immediate operation was 7 per cent, and there was a slightly smaller number of cases in which operation was done immediately than in which it was deferred.

Deferred operation. In 79 cases, operation was deferred beyond six hours from the time of admission; in over half (54 per cent), the period of observation was under four days, and in the remainder it was over four days, extending as long as twenty-eight days in 1 case. The significant fact about the mortality rate of 5 per cent in all deferred operations is that 3 of the 4 deaths occurred when operation fell on the fifth, sixth or seventh day of the disease, either because an early case had been delayed too long or because a late case not long enough to exclude it from this relatively lethal period. There was no death in the group of 33 cases in which operation was deferred over four days, and there was no case in which it was established that an undrained abscess spontaneously ruptured into the peritoneal cavity.

Appendectomy versus incision and drainage. The policy of carrying out appendectomy as a primary procedure in slightly less than half (47 per cent) the cases has remained remarkably constant over the years studied, and the mortality rate for the 104 cases so treated was 8 per cent. It was accepted as a general surgical principle by the members of the staff during the years under consideration that operation should consist of incision and drainage alone, unless it was believed that the appendix could be removed without adding appreciably to the risk of the procedure. It is obvious from a review of the operative notes that there was a disregard of this principle in a considerable

number of cases in which a mistaken sense of pride in securing the appendix at all costs led the surgeon to persist unduly long, or with an unwarranted amount of trauma.

In 10 cases in which no drainage was instituted, the mass made out preoperatively either proved to consist of an indurated portion of the omentum without associated frank pus (8 cases) or was incorrectly taken to represent cancer at the original operation (2 cases). In all save these, cigarette drains were placed in the right gutter or pelvis, depending on the extent of the infection. A special effort was made to bring the drains out along the lateral wall of the peritoneal cavity rather than between loops of small intestine, and when some form of rectus incision was used, drainage through a stab wound was not infrequently (12 cases) employed to accomplish this end.

Incision and drainage alone as the original surgical procedure was carried out in 118 cases, with a mortality of 6 per cent, but always with the expectation that the appendix would be removed at a subsequent operation. Although the number of cases within each group is too small for definite conclusions to be drawn, the statistics (Table 7)

TABLE 7. *Comparative Incidences and Mortalities of Primary Appendectomy and of Incision and Drainage in Relation to Duration of Disease.*

DURATION BEFORE OPERATION	NO. OF CASES	INCIDENCE OF PRIMARY APPENDECTOMY*	MORTALITY OF PRIMARY APPENDECTOMY	MORTALITY OF PRIMARY INCISION AND DRAINAGE
days		%	%	%
1 to 4	56	73	2	7
5 to 7	46	43	20	12
8 or over	120	36	7	4
Total	222			
Averages		47	7.7	5.9

*All the remaining cases had primary incision and drainage.

suggest that the removal of the appendix within the first four days of the disease tends to lower the mortality in a majority of these cases. Furthermore, although removal of the appendix after the fourth day adds materially to the risk, the high mortality rate when operation is done on the fifth, sixth or seventh day of the illness is accounted for not so much by the type of operation that is carried out as by the unfortunate period selected for surgery. In the significantly large number of cases in which operation was performed after the seventh day (120 cases), removal of the appendix as the original procedure nearly doubled the operative mortality, increasing it from 4 to 7 per cent.

Technical Factors

Type of incision. There has been a marked increase in the use of the McBurney incision or one of its modifications at our hospital in recent years with the belief that the danger of contamination of the general peritoneal cavity is minimized through a lateral approach. The striking finding (Table 8) that the mortality rate was less than

TABLE 8. *Influence on Mortality Rate of Type of Incision at Original Operation.*

TYPE OF INCISION	APPENDECTOMY		INCISION AND DRAINAGE		TOTAL OPERATIVE MORTALITY
	NO. OF CASES	MORTALITY	NO. OF CASES	MORTALITY	
		%		%	%
Right rectus	89	9	45	11	10
McBurney	15	0	73	3	2
Totals	104		118		
Averages		7.7		5.9	6.7

one fourth as high when such an approach was used instead of some form of rectus incision seems to substantiate this opinion. We believe, however, that the arbitrary selection of any one incision for all cases is unfortunate, and that the avoidance of unnecessary surgical trauma within the peritoneal cavity in certain cases can best be accomplished through a pararectus incision, with drainage through a stab wound in the flank.

Anesthetic. Local anesthesia was rarely used for appendectomy but was deemed the anesthesia of choice for over one quarter (28 per cent) of the patients in whom incision and drainage alone was carried out. Although ether was the agent used in over half (57 per cent) the entire series, there has been a growing tendency in more recent years toward the use of spinal anesthesia if these cases are not suitable for local novocain infiltration. The fact that the mortality rate (13 per cent) was over twice as high when local anesthesia was used as that (5 per cent) when either ether or a spinal anesthetic was employed merely emphasizes the fact that novocain infiltration was employed in a larger percentage of the poor-risk cases.

Chemotherapy. Chemotherapy was available in only the latter part of the period under discussion, and although we are now employing it routinely in patients with appendiceal peritonitis, it was used in but a single case of this series with mass formation.

Secondary Operation

There were no fatalities in the 76 explorations done as a secondary procedure following incision and drainage of the peritoneal cavity. In 73 of these, appendectomy was carried out between four and seven months after the first operation, and in the remaining cases, there was an almost even division between those in which the interval was under four months and those in which it was over seven.

In slightly over half (55 per cent) the cases, the secondary operation averaged forty-nine minutes,

and it was apparent from a study of the surgeon's notes that the removal of the appendix was technically a relatively simple procedure; in the remaining cases, not including those complicated by such additional surgery as the repair of a hernial defect, the operation was difficult and averaged seventy-four minutes.

We were especially interested in trying to find some correlation between the lapse of time between operations and the relative ease with which secondary appendectomy could be carried out, but could discover no consistent relation between these two factors.

Although we believe that, as a general rule, appendectomy following preliminary incision and drainage should be urged as a secondary procedure to prevent recurrence of further trouble, there were 11 patients in whom, because of advanced age or poor general condition, it seemed wiser to abandon the idea of further surgery. Eight of these patients were over sixty years of age, and of the remaining 3 in their late fifties, 1 was a cardiac and another a diabetic patient. Information is not available concerning the ultimate course of these and the 24 additional patients who failed to carry out our instructions to return for secondary appendectomy.

Complications

Complications, excluding an indeterminate degree of peritonitis, which might be considered an inherent part of the original lesion, occurred in over one quarter (28 per cent) of the total series and one third (37 per cent) of the fatal cases. The difference in the incidence of cases with complications following appendectomy (23 per cent) and those with incision and drainage alone (32 per cent) was accounted for by the larger number of incisional hernias found after the latter type of operation.

The ultimate significance of the high incidence of hernias (16 cases) is qualified by the fact that satisfactory repair at the time of secondary appendectomy was effected in 9 out of 13 cases. It is worthy of note that the incidence of these hernias was higher when the McBurney incision was used for simple incision and drainage (12 per cent) than with some form of rectus approach (9 per cent).

Pulmonary disease was encountered postoperatively in 20 patients, in 2 of whom it was a contributing cause of death. The remaining 18 patients survived despite the postoperative clinical findings of atelectasis (13 cases) and pneumonia (5 cases). Although the former did not retard the patient's convalescence, the latter increased by over one week (nine days) the average time required in the hospital.

Major wound sepsis occurred in 10 cases. The average hospital stay of the survivors was lengthened from an anticipated twenty to forty days, but the only death was in a patient who also had a subphrenic abscess. One other nonfatal subdiaphragmatic abscess occurred.

Residual abscesses were noted in 10 cases and, when they did not subside (4 cases) or rupture spontaneously into the rectum (1 case), required secondary drainage by either an abdominal (2 cases) or rectal (2 cases) approach. In 1 of these cases complicated by further chronic sepsis, the patient died after fifty-four days.

The recorded occurrence of fecal fistulas in 11 cases undoubtedly referred in some to the persistent drainage of pus beyond the anticipated time rather than to the presence of a true fistula. In but a single case was it necessary to operate on a patient to correct this condition.

Although the Miller–Abbott tube was not available during the earlier years of this series, there were but 2 cases in which intestinal obstruction requiring corrective surgery developed.

Other complications encountered were phlebitis (3 cases), postoperative hemorrhage (2 cases), parotitis (2 cases), cystitis (1 case) and pylephlebitis with multiple liver abscess (1 case). Although these complications lengthened the hospital stay appreciably, only the patient with pylephlebitis succumbed.

Cause of Death

In only 1 case with multiple liver abscesses secondary to a pylephlebitis and another with uremia could it be established with any degree of certainty that death had occurred from causes other than a spread of infection in the general peritoneal cavity. The following clinical review of the deaths in this series correlated with the statistical data affords the most constructive approach to a lowering of the mortality rate.

Preventability of Deaths

Errors in Diagnosis

One patient who was sixty-three years old and very ill might have survived had his infection not been disseminated by operation based on the mistaken diagnosis of cholecystitis.

Incorrect Choice of Treatment

Although each case must be judged as an individual problem, we wish to point out that in 6 cases the selection of the fifth, sixth or seventh day for surgery seems to us unwise in the light of our experience.

One of these patients was considered very ill on entry, but nevertheless surgery was not deferred and the patient died of general peritonitis and a complicating pneumonia fifteen days after operation. None of the remaining 5 patients were very ill on admission, and yet 3 died of general peritonitis within three days following operation. The remaining 2 survived their first few postoperative days only to succumb at a somewhat later date to prolonged intraperitoneal sepsis.

In 4 of these last patients, primary appendectomy rather than simple incision and drainage was performed, and thus it appears that the operation selected in all but 1 case was of the type that carried nearly twice as high a mortality for this stage of the disease as the alternative form of surgery.

Errors in Technic

Four patients who were not very ill on admission were operated on at a theoretically favorable period of their disease; yet all of them died of general peritonitis within five days of operation. None of these procedures were unduly protracted, and the implication is that the operative technic was primarily at fault.

Unavoidable Deaths

One of these 5 patients, previously mentioned as having an appendiceal abscess as an incidental and unsuspected finding at autopsy, entered the hospital in a moribund condition and promptly died of uremia without operation. Another patient had a protracted hospital stay of sixty days and finally died of multiple liver abscesses secondary to pylephlebitis. The 3 remaining patients fell into the very young or very old age groups. All were very ill on entry, and it would have been difficult to have improved the treatment that was instituted.

So long as the diagnosis of appendicitis continues to be deferred until perforation has taken place, a group of patients will persist whose deaths may be said to be "unavoidable" only so far as the term refers to a condition that has become established as a result of erroneous earlier diagnosis and ill-advised treatment.

Conclusions

The following conclusions seem justifiable:

Patients with appendiceal peritonitis with mass formation present a very different clinical entity and therapeutic problem from those found in cases of appendiceal peritonitis without mass formation. The treatment in such cases is surgical.

Operations should rarely be done on the fifth, sixth or seventh day of the disease.

If a policy of deferring operation is adopted, it had best be pursued for at least four days.

The abdomen in all cases of appendiceal peritonitis should be carefully palpated under anesthesia before operation, and if a mass is discovered at that time, the plan of treatment should be re-evaluated and operation possibly postponed.

If the presence of a laterally situated mass is not appreciated until after the peritoneal cavity has been opened, any medially placed original incision should be closed and drainage instituted through a McBurney incision.

A McBurney incision or one of its modifications, rather than some form of rectus approach, should be used for both appendectomy and simple incision and drainage, unless the mass lies unusually far toward the midline, when operation through a pararectus incision, with drainage through a laterally placed stab wound, should be considered.

Incision and drainage alone should be done as a primary procedure unless the technical removal of the appendix can be readily accomplished. Observance of this principle is especially important after the fourth day of the disease.

Appendectomy should be carried out within six weeks following incision and drainage unless the patient is in generally poor condition or some complication provides an indication for a longer interval between operations.

Even when a localized mass has formed, the general clinical impression that the patient creates at entry of being very ill or not very ill is of more reliable prognostic significance than any laboratory data.

RETINAL LIPEMIA AND VISUAL DISTURBANCES ASSOCIATED WITH ACROMEGALY AND DIABETES MELLITUS

Report of a Case

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THE following case of acromegaly with diabetes mellitus and retinal lipemia was studied in the Eye Department and also in the Medical Department at the State University in Istanbul, Turkey. It is reported because of its ophthalmologic and endocrinologic interest and because of its clinical bearing on the experimental work in this field.

CASE REPORT

A 35-year-old man was admitted to the Eye Clinic on April 16, 1939, almost blind. He was over 6 feet tall and was definitely acromegalic. Examination and history pointed to a tumor of the hypophysis. The patient suffered from polyphagia and polyuria; there was complete disappearance of the libido, and x-ray study showed a markedly enlarged sella turcica. Four months previously, he had an illness with fever, and sugar was found in his urine. There was a slight odor of acetone to his breath.

There was a certain amount of exophthalmos in both eyes. Ophthalmoscopic examination showed a definite retinal lipemia, but no other abnormality.

The vision was reduced on both sides to seeing movements of the hands. On the right, a field could not be taken; on the left, in the upper nasal quadrant, a small area of the nasal field still remained. Diastolic pressure in the retinal vessels was 40 mm. of mercury on both sides, with a general blood pressure corresponding to the patient's age.

TABLE 1. *Blood Chemical Findings.*

DATE	TOTAL FAT	CHOLESTEROL	BLOOD SUGAR
	mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*
April 24	6800*	710	390
May 10	6400	630	490
May 27	390	440	370

*Normal, 500 to 800 mg. per 100 cc.

The sugar and fat content of the blood is shown in Table 1.

There was 3.3 per cent sugar in the urine, but no albumin or acetone.

The basal metabolic rate was normal.

The patient was transferred to the Medical Department on April 22, and 5 days later he was started on insulin (the first 2 days, 40 units; then, 100 units daily) and diet.

By May 5, his general health had improved markedly; his color was much better, and he was cheerful. Vision in the right eye was 1/25, and in the left eye 5/35. There was definite improvement of the nasal part of the visual fields. However, the findings in the blood and urine remained unchanged.

On May 8, in addition to the insulin, posterior pituitary extract was given parenterally. On May 18, vision on both sides had improved to 5/10 in both eyes. The nasal part of the visual fields was almost normal, a bitemporal hemianopia being present. The sugar content in the urine, however, had not changed. The ophthalmoscopic findings were normal.

On May 20, the insulin was omitted, but the pituitary extract was continued.

On May 31, the patient did not feel well, and the eyes showed a turn for the worse; the vision in the left eye had decreased to 5/20; in the right it was 5/6. The sugar in the urine varied between 2.3 and 3.1 per cent.

On June 3, all medication was discontinued. On June 12, there was a further decrease in vision: 5/10 in the right eye, and 5/35 in the left. The nasal parts of the fields were again somewhat involved. The patient had lost 4 pounds. Two days later, the general condition was worse. Vision on the right was 5/20, and on the left 1/10. Ophthalmoscopic examination showed a return of the lipemia as seen in the beginning. Between June 3 and 13, the sugar in the urine remained unchanged.

On June 13, a course of x-ray treatment was given to the pituitary gland, and on June 25, the general condition was again improved. Vision went up to 5/7 on the right and 5/20 on the left. There was bitemporal hemianopia. On July 11, vision was 5/7 on the right and 5/15 on the left. The fields were unchanged, but the patient could occasionally see some movements in the temporal fields. The lipemic condition in his eyes had again disappeared.

The patient was discharged on July 15. He did not return for further x-ray treatment.

A diagnosis of tumor of the pituitary gland, complicated by diabetes mellitus, was made. There was no increase in the excretion of nitrogenous substances, no ketonuria and no ketonemia. Most remarkable was the increase of total fat and cholesterol in the blood, and in connection with this general hyperlipemia, there existed a very marked retinal lipemia. Besides the retinal change, the patient showed other unusual eye disturbances.

The retinal lipemia in this case was absolutely characteristic. It is not necessary to describe the clinical picture fully, since many descriptions and pictures are available in textbooks and other publications.

DISCUSSION

It is well known that glycosuria and even severe diabetes, with and without coma, may occur with acromegaly. The relation of the pituitary gland to the carbohydrate metabolism was clarified by clinical studies and the fundamental experimental investigations of Cushing and Davidoff,[1] Houssay

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and Biasotti,[2] Young[3–5] and others. According to the recent studies of Best et al.[6, 7] and of Young, there is no pituitary diabetes without involvement of the pancreas. After injection of anterior-lobe extract, with resulting diabetes, an extensive fall in the insulin content of the pancreas and microscopic changes in the islands of Langerhans were noted. One must assume that the pancreatic disease and the lack of pancreatic hormone can be caused by a hypersecretion of pituitary diabetogenic hormone.

The relation of the pituitary gland to fat metabolism is not so clear as that to carbohydrate metabolism. The assertion of Anselmino and Hoffmann[8] and Raab[9] that substances secreted by the pituitary influence the fat metabolism is not yet proved.

Has pituitary diabetes any characteristic features of regular diabetes? Clinically, von Noorden[10] has pointed out that the glycosuria of patients with acromegaly is not influenced so easily by change of diet as the ordinary diabetes is. Alternating hyperglycemia and hypoglycemia in rather sudden changes was seen by Goldschmidt.[11] His case showed acromegalic symptoms and bony destruction of the sella without enlargement; at autopsy, no lesion of the pituitary gland was found even on microscopic examination. According to Joslin et al.,[12] the diabetes found in acromegaly or other pituitary disease does not differ essentially from ordinary diabetes, but it varies from time to time according to the activity of the hypophysis, and as a result a spontaneous temporary or permanent cure of the pituitary diabetes may be effected. Oppenheimer[13] described a patient with coma who after a certain time showed a surprisingly high tolerance for carbohydrates.

The response to insulin seems to be of a certain importance in the differential diagnosis between pituitary and ordinary diabetes. Ulrich[14] pointed out that insulin is less effective in pituitary diabetes and recommended its use to differentiate pituitary from ordinary diabetes. This clinical experience was supported by experimental results.

The retinal lipemia in the case presented in this paper was, in its ophthalmoscopic appearance as well as in its response to insulin, similar to the published cases of retinal lipemia, none of which showed pituitary symptoms. The decrease in blood sugar and blood lipids, however, was much quicker and more marked in most of the published cases. One can say that in the case presented above there was some resistance against insulin, especially so far as the sugar was concerned, and it seems possible that the involvement of the pituitary gland had something to do with this resistance. But it must be said that in McCann's[15] case, which was supposedly due to an ordinary pancreatic disease, the retinal lipemia disappeared in seven to nine days, whereas both the sugar and the lipids in the blood increased during this time under treatment consisting of 10 to 30 units of insulin a day.

After the insulin was stopped, the patient in the case discussed above became worse in every respect, and retinal lipemia recurred; however, when x-ray therapy was given to the pituitary region, all symptoms improved, and the retinal lipemia disappeared. This indicates that the pituitary lesion was related to the diabetes and especially to the retinal lipemia.

Concerning the visual disturbances, two questions arise. What was the reason for the almost total blindness of this patient? And was the involvement of the nasal fields due to the same source that caused the involvement of the temporal fields?

It would be easier to understand the total blindness if one could assume that the retinal lipemia had, because of impaired nutrition, an injurious effect on the retinal tissue. Reis[16] made such a suggestion, but his case was probably complicated by disease of the optic nerve. There is no doubt that most patients with characteristic lipemia who were tested for visual disturbances had normal function (Turney and Dudgeon,[17] Koellner,[18] Moore,[19] Hardy,[20] McGuire,[21] Wagener,[22] McCann,[15] McKee and Rabinowitch,[23] Chase[24] and Jaffe and Schonfeld[25]).

In some apparently uncomplicated cases, blurred vision or a slight decrease of visual acuity was found (Darling,[26] Rowe[27] and Ferber and Apperman[28]). Only Ferber and Apperman mention that the visual trouble ceased after disappearance of the retinal lipemia. Machlis's[29] patient suffered from diabetic coma with retinal lipemia; when the patient recovered from the coma, he was "virtually blind," but the retinal lipemia subsequently disappeared, with a full return of the visual capacity. This case, complicated by a transient coma, cannot be compared with a case like the one presented above.

It is true that in this case the improvement of the retinal functions was simultaneous with the disappearance of the retinal lipemia and that the decrease of the vision after the insulin was stopped was accompanied by a recurrence of the retinal lipemia. Nevertheless, I cannot believe that the functional disturbance was produced by the lipemic state of the retinal vessels, because in most cases, the lipemia is harmless to the retinal tissue, and it is quite unlikely that in a few exceptional cases the retina could be damaged by lipemia. Furthermore, the effect of x-ray treatment cannot be explained by the assumption that the visual disturbance was caused by retinal disease.

It seems more probable that the effect of both therapeutic agents (insulin and x-ray) was due to their influence on the pituitary-diencephalic region. The pituitary tumor was responsible only for a bitemporal hemianopia, which was very resistant to treatment. Perhaps a second series of x-ray treatments would have brought some results, because after the first there was a slight improvement. It is quite unlikely, however, that the involvement of the nasal visual fields was due to a growing tumor, because in such a case the involvement of the uncrossed chiasma fibers occurs at a relatively late stage, when there is already an optic atrophy. The disks in the patient under discussion were absolutely normal, and the prompt success of the insulin therapy is not in favor of such an assumption.

It is more probable that besides the tumor pressure another process was present in the pituitary-diencephalic region and that this process caused a temporary interruption of the whole optical pathway on both sides. It was influenced by insulin as well as by x-ray therapy, as demonstrated by the improvement of the central and peripheral vision. But the improvement of the peripheral function was seen only on the nasal fields, because the temporal fields (the crossed nerve fibers) were blocked by the tumor pressure. I assume that the tumor hemianopia was superimposed on the other disturbance, which involved nasal and temporal fields at the same time — in other words, that there were two different conditions acting at the same time on the eye apparatus in the chiasmal region. Whether besides the tumor pressure there was an influence on a center in the pituitary gland or somewhere else in the diencephalic region, I do not know. One can be quite sure that the initial improvement, then deterioration and then improvement again were not mere accidents, since the turn for the worse started again as soon as the insulin was omitted.

Some experiences of Zondek[30] and Feigenbaum[31] are notable. The former has drawn attention to a condition that he calls "salt-water obesity." The main symptom is chronic headache, which, according to him, is due to an increase of cranial pressure; he believes that this increased pressure is caused by a retention of water and salts in the cerebral tissue. The localization of this condition in the vicinity of the chiasm could be considered probable by bitemporal hemianopic defects (according to Feigenbaum) that disappeared as did the headache after dehydration therapy and other measures causing the removal of the salts. In Zondek's case, in which the sella turcica was enlarged and there were genital symptoms besides the headaches, the bitemporal hemianopia for colors also disappeared after such therapy. This fact showed, according to Zondek, "that not only the pressure of a growing tumor (probably a chromophobe adenoma) caused the changes in the field of vision, but that also processes responsive to therapy, in the vicinity of the tumor, were causative factors."

These observations of Zondek and Feigenbaum and the case reported are different in many respects, but they seem to have one point in common: that pituitary disease may influence the optic pathways not only directly by the pressure of an existing tumor but also in a more indirect way. If this could be confirmed by further observations, it would be interesting from an ophthalmologic as well as from an endocrinologic standpoint.

Summary

A case of acromegaly complicated by diabetes mellitus with retinal lipemia and peculiar visual disturbances is described and discussed.

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CLINICAL NOTE

HAMARTOMA OF THE SPLEEN: REPORT OF A CASE

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A RECENT experience with a case of hamartoma of the spleen, because of the rarity of the condition, prompts us to report this case in some detail.

There are few references to this tumor in the literature, and the standard textbooks of pathology refer to it only briefly. Hamartoma is a tumor composed of tissue, present in excess beyond normal requirements, that can hardly be distinguished from the normal but possesses a limited capacity for aberrant growth. These tumors are benign and clearly demarcated, and often attain a fairly large size. To those of the spleen, the term "splenoma" has been applied. The age of the patient varies. The tumor is probably of congenital or of embryonic-rest origin, and usually attracts attention only by its size. In 6 patients—4 men and 2 women— reported by Mordasini,[1] the ages ranged from twenty-three to eighty-four years. In all, the spleen was enlarged with a clearly demarcated mass or masses that simulated the splenic tissue, but varied in details of histology and arrangement. The only symptoms were those of splenic enlargement. Apparently, the function of the organ was not disturbed. In Fischer's[2] case, that of a forty-two-year-old man with splenic enlargement, the spleen weighed 2100 gm. These tumors have occurred in animals[3] as well as in human beings.

The description and illustration of the histologic findings in this case may help to further the understanding of this rare splenic tumor.

CASE REPORT

Mrs. J. F., a 59-year-old Italian-born housewife, was referred to the clinic of the Palmer Memorial Hospital because of swelling of the abdomen. She had been obese as long as she could remember, but stated that since 8 months previously her abdomen had been growing disproportionately larger. She had consulted a chiropractor first, but failing to obtain relief had gone to her regular physician, who discovered that she had an abdominal tumor. It was also discovered that she had diabetes; she had never taken insulin, however. During the previous 4 months, she had become unusually costive, having to resort regularly to the taking of laxatives.

The patient had had no serious illnesses and no operations. She had been married for 38 years and had had thirteen children, of whom eight had died in infancy or childhood. She had had four miscarriages. She had had no menstrual periods for several years and had had no vaginal bleeding or discharge.

Physical examination showed a short, obese woman weighing 186 pounds—17 pounds less than she had weighed 6 months previously. The heart appeared normal, except for a soft, blowing systolic murmur over the entire precordium. The blood pressure was 120/80. In the left side of the abdomen was a large, firm tumor mass about 25 cm. in diameter. It was easily moved about, but not so freely as many ovarian tumors of that size. Its chief point of attachment was apparently in the upper quadrant rather than in the lower. Bimanual examination of the pelvis revealed a prolapsed but otherwise not abnormal uterus. There was no demonstrable connection between the tumor and any of the pelvic viscera.

Laboratory examinations revealed a red-cell count of 3,730,000 with a hemoglobin of 67 per cent, and a white-cell count of 8750 with 76 per cent polymorphonuclears, 16 per cent lymphocytes, 7 per cent large mononuclears and 1 per cent eosinophils. The platelets were normal, and the red cells showed slight poikilocytosis and anisocytosis. The blood sugar was 110 mg., and the cholesterol 141 mg. per 100 cc. The blood Hinton reaction was negative, and the urine was essentially normal.

X-ray examination showed a large mass, approximately 17 cm. in diameter, in the left side of the abdomen, with its medial border at the lateral psoas margin and its lower border just below the iliac crest. Its outline was relatively smooth.

A preoperative diagnosis of cyst of the spleen was made, and splenectomy was performed on August 2, 1940.

The abdomen was opened through a long, left rectus-splitting incision. The tumor was about the size of a large grapefruit and lay in the substance of the spleen. It felt soft, as though it might be a cyst or perhaps a large hemangioma. It involved the lower but not the upper pole. The vessels of the splenic pedicle, which were very large, were cut between hemostats and tied with a heavy silk ligature. The smaller vessels along the lateral margin and the vasa brevia were tied separately with chromic catgut. There was practically no bleeding during the operation. After it was made certain that the vessels were securely tied, the rest of the abdomen was hastily explored, but nothing abnormal was found except that the gall bladder was distended and contained stones. There was one large stone impacted in the ampulla. Nothing was done about the gall bladder, and the wound was closed in layers in the usual way.

During the first few days, the patient had a moderate elevation of temperature, with a cough and thick yellow sputum due to partial atelectasis at the bases of both lungs.

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By the end of a week, this had all subsided, and the convalescence from that time on was completely uneventful. The wound healed well. The patient was discharged on the 16th day after operation.

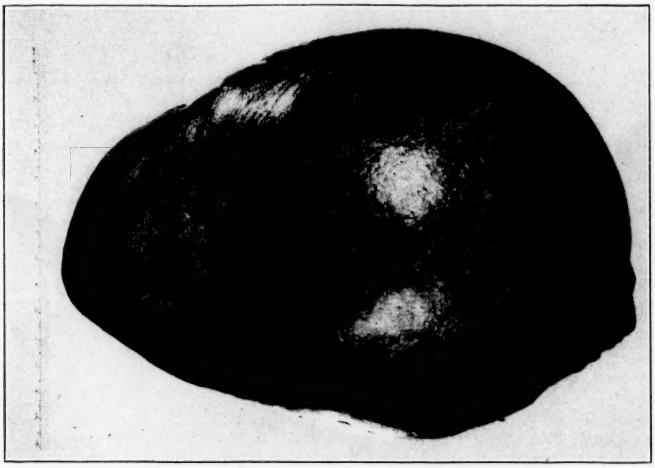

FIGURE 1. *Surface of Spleen, Showing Circumscribed Character of Nodule.*

Pathological report. The specimen consisted of a spleen weighing 1120 gm. and measuring 23 by 17 by 7 cm. The surface was smooth, glistening and reddish gray. The lower two thirds was bulbous, with prominent capsular veins. The consistence was almost cystic; the tissue at the upper pole was moderately firm. On cut section, the lower two thirds was well demarcated, but not separated from the remaining normal splenic tissue by a clearly defined capsule. The tissue here was deep brownish red and finely trabeculated, and showed small vessels, as well as ill-defined malpighian follicles. The rest of the spleen was normal in color and showed normal trabeculations and malpighian corpuscles. Microscopically, the splenic tissue proper was not remarkable, although somewhat hyperemic. Within the encapsulated nodule, there was an irregular increase in fibrous stroma and some replacement of the pulp by fibrous tissue. The structure of the sinusoids, trabeculae and malpighian follicles was fairly well maintained. A few plasma cells were present

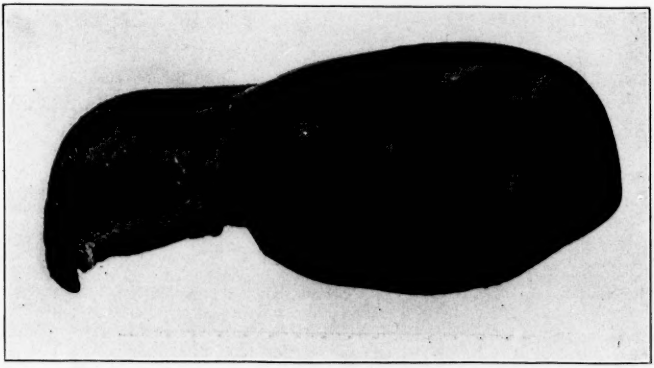

FIGURE 2. *Cross Section of Spleen, Showing Resemblance of Tumor to Splenic Pulp.*

about some trabeculae. Rare foci of erythropoiesis occurred in the tumor. The hamartoma was not clearly encapsulated, but was of even contour and sharply defined from the normal splenic tissue, and had an incomplete pseudocapsule made up of compressed trabeculae. In the hamartoma, the malpighian corpuscles were present, but ill defined. There were scattered megakaryocytes in the pulp. Many of the sinusoids were fairly heavily congested. Diagnosis: hamartoma of the spleen.

Summary

A case of splenic tumor due to hamartoma is reported. This is a benign congenital neoplasm reproducing the structure of the spleen.

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MEDICAL PROGRESS

ENDOCRINOLOGY: TREATMENT OF ABNORMALITIES OF THE ANTERIOR PITUITARY GLAND

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BOSTON

THE anterior pituitary gland, by means of its secretion of tropic hormones, directs growth, regulates the activity of the adrenal cortex and the thyroid gland, stimulates the gonads and leads the ovaries through their complicated cycles, influences carbohydrate and probably protein and fat metabolism and takes on the additional task during pregnancy of influencing mammary development and function. The peripheral endocrine glands, stimulated by the pituitary secretions, form their specific hormones, which not only exert widespread actions but also effect and determine the further activity of the pituitary gland. A dynamic and orderly relation exists, which is not a true equilibrium, since the whole system is continually altering or readjusting itself. This discussion is limited to the treatment of disorders of the anterior pituitary gland that upset its normal relations.

Disorders of hypoactivity result when the pituitary gland diminishes its control over a single or a group of peripheral endocrine glands (as in Simmonds's disease), or when the peripheral gland is diseased, absent or unable to respond regardless of pituitary prodding—as the ovary acts during the menopause. Treatment can be stimulatory by means of specific pituitary hormones if the target gland is capable of responding, or by means of substitutive materials that replace the secretion of the target gland if that organ is not capable of responding. Pituitary hyperactivity may goad the peripheral organs on to renewed and excessive activity, as in acromegaly, or the end organs may get out of hand and set up autonomous control, as in primary adrenocortical tumors. Treatment consists of surgery, x-radiation or the use of hormones or other substances to alter the internal milieu leading to a suppression of the overactive gland or to a possible diminution of the activity of its hormones. The more important materials and methods available for treatment are discussed below.

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Available Methods of Treatment

Pituitary and Related Hormones

Attempts to make the various fractions of the pituitary gland available for treatment have been extensive, but numerous technical difficulties exist. The gland does not store its secretion in quantities, since its hormones may be elaborated only as needed, and large numbers of glands are necessary to obtain a useful amount of hormone. The number of pituitary hormones that exist is uncertain, but they appear to be numerous. They are probably protein substances, and it is proving very difficult to devise technics for separating, extracting and purifying them without alteration or loss of potency. Finally, since they have not been characterized chemically, biologic assay is necessary. This is usually involved, expensive and difficult to interpret, and often requires considerable amounts of the hormone to be tested. Also, bioassay is not a certain means of establishing the individual identity of a hormone, since the same substance may give multiple effects. Owing to these impediments, progress has been slow.

Extraction for pituitary secretions is usually done in aqueous, acid or alkaline solutions.[1] The hormones may be precipitated by organic solvents, or by the use of increasing concentrations of salts at

TABLE 1. *Present Status of Purified Pituitary and Related Hormones.*

HORMONE	ACTION	POTENCY OF PURIFIED PREPARATIONS *per mg.**	CONTAMINATING HORMONES	MOLECULAR WEIGHT	OBSERVATIONS ON PROTEIN	OBSERVATIONS ON CARBOHYDRATE	OTHER CHARACTERISTICS
Follicle-stimulating hormone (FSH)	Stimulates follicle growth in the ovary and spermatogenesis in the testis	200 rat units[2]	Slight amount of LH[2]	Not available	Only pituitary hormone in the albumin fraction[3]	4.5%[5] to 18.7%[6] carbohydrate, probably mannose; amylase will destroy hormonal activity[4]; 4.4%[5] to 8.0%[6] hexosamine.	Probably has an –S–S– (disulfide) linkage
Luteinizing hormone (LH) or interstitial-cell-stimulating hormone (ICSH)	With FSH, causes ovulation and corpus-luteum formation; stimulates interstitial tissue of the male and female gonads.	200[7] to 500[8] rat units	None[2]	About 90,000 in the pig[9]; 40,000 in the sheep.[7]	Contains 1.0% tryptophane in the sheep[7] and 3.8% in the pig[9]	2.8%[5] to 4.45%[7] hexose, probably mannose; 2.2%[5] to 3.8%[6] hexosamine.	Probably has an –S–S– linkage
Pregnant-mare serum (PMS) or equine gonadotropin	Stimulates follicle formation and luteinization	4000 to 7000 rat units[10]	None	Calculated to be 30,000[11]	Contains tyrosine and tryptophane[11]	14.1%[11] to 17.6%[5] hexose, probably galactose; 8.4% hexosamine.[5]	Activity is destroyed if the free amino groups are blocked out.[11]
Chorionic hormone of pregnancy urine (APL)	Probably is a luteinizing and interstitial-cell-stimulating hormone	8000 rat units[12]	None	About 100,000[12]		10 to 12% hexose, probably galactose[5]	Activity is not destroyed if the free amino groups are blocked out.[11]
Lactogenic hormone	Maintains lactation; stimulates the crop gland in the pigeon.	10,000 local pigeon units[13]	None	About 26,500[14]	Contains tyrosine and tryptophane[15]	No carbohydrate	Activity is destroyed if the free amino groups or tyrosine is blocked out.
Growth hormone	Maintains growth in hypophysectomized animals	100 hypophysectomized-rat units[2]	Slight amount of thyrotropic hormone[2]	Not available	In the euglobulin fraction[16]	Almost free of sugar[3]	Not inactivated by cysteine, and there is probably no –S–S– linkage.[3]
Thyrotropic hormone	Stimulates the thyroid gland	150 chick units[17]	Slight lactogenic, adrenotropic, growth and FSH activities; considerable LH.[17]	Not available	In the euglobulin fraction[16]	3.5% hexose; 2.5% hexosamine.[17]	Probably has an –S–S– linkage[17]
Insulin[18]	Lowers blood sugar; exerts antidiabetogenic action.	24 international units	None	20,000 to 37,000	Typical protein; amino acid constituents have been almost completely analyzed.	None	3.2% sulfur; contains an –S–S– linkage; x-ray diffraction patterns show it to be similar to most proteins.

*The unit of each pituitary hormone, when accurately noted, has an involved definition because conditions of bioassay must be clearly delineated. It is therefore not possible to present these details here, but one unit is usually the amount that will produce the minimal detectable response in the particular end-organ measured in a given species of animal. The test animal used is noted on the chart, but the unit for a given hormone is of no comparative value with that of any of the other hormones.

varying hydrogen ion concentrations. After selective precipitation of each fraction, methods are available to inactivate the contaminating substances, leading to a more homogenous preparation of the desired hormone. This relatively purified material is then bioassayed by numerous technics to determine the amount of the desired hormone and the presence of active hormonal contaminants. Some of the pituitary hormones have been analyzed chemically, and their reactions to different materials studied. They have been examined by electrophoresis and in the ultracentrifuge to determine their homogeneity and molecular weight. By these procedures, the growth, thyrotropic, adrenotropic, lactogenic, follicle-stimulating and luteinizing secretions of the pituitary gland have been isolated and studied. Similar observations have been made on the chorionic hormone of pregnancy urine and on the equine gonadotropin found in pregnant-mare serum. Table 1 shows the present status of these substances. It is of interest to compare these observations to what is known of insulin, a protein hormone that has been available in large quantities in crystalline form for about fifteen years.

There has been some hope that the various pituitary hormones represented prosthetic groups, which were relatively simple, ultimately synthesizable molecules attached to a protein carrier — for example, thyroxine on a globulin. This has not been proved, and the pituitary hormones appear to be individual homogenous proteins. Extraction is difficult, the hormones are not attainable in large quantities, and synthesis appears remote. Unless available sources for these materials improve, as those of the chorionic and equine gonadotropins have, hope for adequate, clinical pituitary therapeutic agents is scant.

Another obstacle in the use of pituitary substances is that they all seem to stimulate in the host the formation of substances referred to as antihormones, which neutralize their activity. The literature has been adequately reviewed,[19, 20] and the general opinion formed that antihormones are immune bodies developed against proteins, either those extracted with hormone or the pure exogenous hormone itself. There is at present no evidence that patients injected with and refractory to pituitary hormones inactivate their own secretions.[19] Although it has been observed that the purer the pituitary hormone the less the antihormone formation, it is not likely, because of species differences, that the very pure preparations will give no antihormone formation. At least in the luteinizing[7] and lactogenic hormones,[15] species differences in even the most purified preparations have been found. From a practical point of view, three to six weeks after the continued administration of a pituitary hormone, the antihormone titer gradually increases until the hormonal effect is completely neutralized. When the treatment is stopped, the antihormone titer usually disappears almost as rapidly.[19] Pituitary and related hormones should therefore be given in courses of six to eight weeks, followed by rest periods of similar duration. Gradually increasing amounts during a given course and alternation of the type of pituitary preparation, in both the animal source and the method of extraction, may diminish the antihormone influence and enhance the efficacy of the treatment.

On the market today are various pituitary and related preparations, mostly in an uncertain state of purification.[21] They deteriorate in aqueous solution on standing, and the dried pituitary powders are more satisfactory for storage. All these materials must be given parenterally, and care for specific sensitivity should be observed, particularly with pregnant-mare serum. The preparations available are as follows:

Whole pituitary substance.

Growth hormone. This is impure and of varying potency, and the usual dose is about 1 to 3 cc. daily to three times weekly.

Lactogenic hormone. Although fairly pure, the hormone has proved of little clinical value.

Thyrotropic hormone. Extracts of this material contain most of the other pituitary hormones, but its thyrotropic activity is usually about 200 chick units per cc. In man, it gives definite effects in responsive thyroid glands, and it is of some value in diagnostic tests in determining the ability of the thyroid gland to respond to pituitary stimulation.[22]

Gonadotropic hormones. Purified pituitary gonadotropins are not generally available, but a pituitary extract (called the synergic factor and said to contain mostly gonadotropic hormone[23]), in combination with the chorionic hormone, is reported to give a marked gonadotropic effect. Otherwise, the chorionic hormone is of little value clinically except in the treatment of selected cases of undescended testes.[24] It is available in solutions containing 100 to 500 international units per cc., the usual single dose. Pregnant-mare serum is a potent gonadotropin, but its usefulness is disputed. It is available as a powder and can be made up to solutions containing 500 international units per cc.

Each of these gonadotropins has its peculiar properties, and their proper use is most complicated and not well understood. When they are given sequentially or coincidentally or when estrogens are added, augmentation and modified effects are observed. These hormones may be eminently satisfactory when their technic of use is clarified, and they can be given with some hope of anticipating the result. At present, indications for their use are very limited.

Substitutive Therapy

In contrast to the rather gloomy pituitary picture are the brilliant successes attending the isola-

tion, purification and in many cases the synthesis of the secretions of the peripheral endocrine organs. Of even greater significance is the discovery of synthetic materials, chemically dissimilar to the hormones but possessing some of their physiologic activities. Today, one may use thyroid, parathyroid, insulin, adrenalin, the various adrenocortical, testicular and ovarian steroids, diethylstilbestrol, methyl-testosterone and dihydrotachysterol to obtain consistent effects that stimulatory treatment will not give. It is impossible to discuss here the extreme ramifications of the use of these substances, except to note that in most cases they are more satisfactory than pituitary hormones, since they are very potent and the dosage can be controlled. They are also relatively inexpensive, and except for parathyroid hormone, produce no significant antihormone effect. The thyroid and some of the steroid hormones, such as testosterone,[25] stimulate the pituitary gland in small doses. Large doses of gonadal hormones, on the other hand, definitely inhibit some of the pituitary activities.[26]

X-Radiation

X-radiation is extensively used in the treatment of overactivity and tumors of the pituitary gland. In the various functional and obscure disorders, the indications, dosages and dangers are not yet clearly defined. Considerable work must be done on the differential susceptibilities to x-ray of the various pituitary functions at different ages and stages of activity. It is well to remember that pituitary activity is of different significance at different ages. In childhood, it is necessary for growth and for stimulating the target glands to the increased activity essential to normal maturation. In adult life, its usual functions are most manifest in the sex cycles and during the alterations of pregnancy and lactation. After the climacteric, this function continues, but some of the target glands fail to respond to the stimulation. In all therapy, these relations to age and function are major considerations and, particularly in the treatment of overactivity of the pituitary gland, should not be neglected. If the most actively functioning cells are those sensitive to x-rays, this is an important point. Studies of the various hormones excreted in the urine after pituitary irradiation, similar to observations following ovarian irradiation,[27] have yet to be done. By the use of surgery, it is obvious that all functions of the pituitary gland may be distorted, but x-ray therapy offers the possibility, although there is no definite proof, of selectively influencing the overactive cells. There are favorable reports on the value of pituitary irradiation in functional menstrual disorders, menopausal syndrome, hypertension, adiposogenital dystrophy, thyroid dysfunction, potential gigantism and other abnormalities,[28–32] but until more is known about the effect of x-ray treatment on the pituitary gland, its general use cannot be advocated. The pituitary functions are too vital for the gland to be indiscriminately exposed to irradiation.

On the other hand, in the treatment of hypophyseal tumors, more radical therapy is justifiable, and x-ray therapy appears to be of great value. About 20 to 25 per cent of all intracranial tumors are of pituitary origin. Approximately three quarters of these tumors are of the nonfunctioning chromophobic type and are fairly sensitive to x-rays, except for the cystic type, which makes up about 14 per cent of the chromophobic tumors.[33] Clinically, these two groups cannot be distinguished, but it is commonly agreed that hypophyseal tumors deserve a trial of irradiation before surgery is undertaken.[34] Although there is some question whether this clinical dictum applies in the presence of serious interference with vision, it has been pointed out that x-ray treatment in these cases is often of as much or as little avail as surgery. Since pituitary tumors have such a varied history, the criterion of successful treatment is not so much the prolongation as the enhancement of life — that is, the remission of symptoms and the salvage of sight. In this respect, x-ray therapy is superior to surgery, since it has no operative mortality and less morbidity.[35] If an adequate trial of x-radiation is unsuccessful and there is evidence of progression of the disease, surgery is advised. If surgery is resorted to, the immediate results and prevention of recurrence are considerably improved by postoperative x-ray therapy.[36]

Acidophilic adenomas are small, grow slowly, and compose 20 to 25 per cent of pituitary tumors. They are functionally active and produce gigantism or acromegaly, depending on the age of onset. These lesions are usually radiosensitive, so that surgery is seldom indicated. Basophilic adenomas, on the other hand, are infrequently seen, but they are responsible for some cases of Cushing's syndrome and their response to x-ray treatment is variable.[31]

X-ray dosages need not be very large, but if response is not satisfactory several courses of treatment are justified.[34] The patient may become weakened and depressed for several weeks after treatment, and symptoms may be temporarily accentuated before improvement begins. Alterations in objective findings, such as eye fields, are not spectacular and may take several months. Recurrences necessitate repeated courses of x-radiation.

Clinical Considerations

Growth

Many so-called "endocrine problems" in childhood leave the therapist in a quandary about whether treatment is justified. A decision must be based on a thorough knowledge of normal

growth and development. The effect of heredity is well known but often not adequately considered. If the patient is found to be large boned, stocky or hirsute, this is perhaps due to heredity and not to the postnatal activity of the endocrine glands. Draper[37] has pointed out the complexity of individual structure and notes that "sex is something more than the mere presence of a gonad." One cannot presume to change the basic stuff of man with hormones. In fact, it appears clear that therapeutic effects from hormones are usually dramatic only when the hormone is needed and that constitutional deviations are not much influenced by their use.

The consequence of environmental, regional, socioeconomic, secular, psychic and medical factors must be understood.[38] For example, the growth of children varies in different regions: children in California are taller than those elsewhere,[39] and great variations appear to be normal in the onset and rate of maturation. Large amounts of data that are essential to help delineate the broad category of normal for each person are being accumulated.[40-42] One must avoid turning a normal child in transition, or a lazy, overindulged person, into an endocrine problem.

Dwarfism

The evaluation of successful therapy necessarily derives from the accuracy of diagnosis. Dwarfism due to chronic disease or nutritional inadequacy requires treatment of the underlying condition, and it is not yet established whether therapy with endocrine preparations influences the growth of such dwarfs. Cretins and hypothyroid children have definite diagnostic criteria,[43, 44] and thyroid stimulates excellent growth so long as the epiphyses of bone are ununited, although the growth factor of the pituitary gland has no effect.[45]

The hypopituitary dwarf (Lorain–Levi type) is delicate, well proportioned and sometimes bright. He has a normal basal metabolic rate, a high sugar tolerance and marked retardation of epiphyseal development, and is neuter in his body configuration and much retarded in sexual development. If possible, treatment should be started early and continued over an extended period. Pituitary growth hormone has been widely used, and although results have been occasionally reported as successful,[46] they are usually variable and inconsistent.[47] The chorionic hormone is probably more useful, apparently inducing a growth response through stimulation of the testes.[48, 49] On the whole, the use of pituitary and pituitarylike hormones to stimulate growth has been a depressing chapter. This may well be due to the quality of hormones available, for the amounts necessary for good effects are large and the antihormones that may develop are very limiting factors. It must be realized that growth is a slow process and that prolonged therapy is essential. We have repeatedly tried to stimulate retarded growth by such therapy and the results have never been dramatic and not much in excess of the growth of preceding years. It appears that the pituitary gland has a highly specific growth hormone, and it is unfortunate that its therapeutic effects are not more obvious in this very important problem. As available hormones improve, better results may be obtained, but at the present time, better stimulation of growth can be elicited by the use of peripheral hormones rather than by those derived from the pituitary gland.

The use of testosterone to stimulate growth is still in the experimental stage, but it seems to be the simplest and most effective way. It may act through a stimulatory effect on the pituitary gland,[25] but it also is probable that it has an immediate specific action in causing nitrogen and calcium retention and in inducing muscle growth.[50] It may be given as testosterone propionate, 10 to 25 mg. intramuscularly twice weekly,[51] or as methyl testosterone, 10 to 25 mg. by mouth daily.[50] The patient should be carefully watched for the occasional undesirable side reactions of the drug, such as hirsutism, macrogenitalism and edema.

Since this treatment is new, several problems must be considered. In striking cases, the appropriate age for starting treatment appears to be early. The hazards of testicular injury, premature closure of the epiphyses and macrogenitalism are more than compensated for by the possibility of removing the patient from the dwarf category. In less obvious dwarfism, it is wiser to delay conservatively because of the striking variations in growth rate that normally develop at puberty. One aid in this decision rests with the skeletal development, which in true pituitary deficiencies is much retarded. So long as the epiphyses are ununited, growth is possible, and the bone age therefore indicates the urgency for treatment. Little growth is to be expected by any therapy after union of the epiphyses. There is some evidence that methyltestosterone is more specific for growth than testosterone propionate,[50] and this suggests the possibility of finding an even more specific growth-stimulating steroid hormone with minimal androgenic activity. The value of simultaneous use of other hormones with testosterone has produced some discussion in the literature. The employment of estrogenic hormones in girls to achieve more physiologic development, the use of simultaneously administered thyroid and the benefit of occasional courses of the chorionic hormone in males to diminish the inhibitory effect of testosterone on the testes must be further studied. The answer to these problems may lead the way to a more promising treatment of pituitary dwarfism.

Obesity of Puberty

The term "Fröhlich's syndrome" to describe the commonly seen obesity of puberty is a misnomer.[52] The patient described by Fröhlich had a tumor at the base of the skull associated with obesity, retarded growth and hypogenitalism. This syndrome is said to be excessively rare: of 140 cases of obesity in puberty reported,[53] not one was a true Fröhlich's. The present tendency is to discard this eponym and divide the obesity problem of puberty into two groups.

It is essential to rule out the very common problem of the fat, overgrown child at puberty. There is often a familial history of obesity, and the condition is equally common in both sexes. The child is often precociously bright and has a smooth, moist skin and obesity of the trunk and mammary glands, with slender extremities. The basal metabolic rate and glucose-tolerance tests are not abnormal, bone development is normal or advanced, and sexual maturity appears at the usual time or earlier.[54–57] These children are often not much concerned about their difficulties and have few subjective complaints, but they are usually overprotected, infantile personalities. This disorder is not regarded as primarily endocrine in nature. It may be due to simple overeating or, as has been theorized, to a functional disorder of the hypothalamus leading to excessive fat deposition. The essential treatment includes diet and psychotherapy, partly of the parents.

The situation in this type of child, however, is not infrequently complicated by a marked retardation of sexual development and sometimes by undescended testes, and the problem then becomes one of a true adiposogenital dystrophy. Such patients may or may not have retardation of bone age and bone growth, a low basal metabolism and a high sugar tolerance. In unpublished work from this laboratory,[58] they all show low excretion rates of the hormones of their sex. Such children represent difficult problems concerning the extensiveness of therapy, for a large percentage of them develop normally later without treatment[59] or may mature promptly with only a reduction of their obesity. Some of them, however, remain sexually underdeveloped and fat, and these represent a serious therapeutic problem.

Treatment should always be dietary, rarely hormonal, because the eventual appearance of sexual maturity is apt to be associated with a spontaneous loss of weight and disappearance of the syndrome. It is not the function of this review to discuss dietetic therapy, but the occasional appearance of hypoglycemia must not be neglected.[60] Aids to diet are amphetamine (Benzedrine) and thyroid. In our experience, thyroid is of considerable help, for it tends to increase vigor and activity; the suggestion, however, that it may stimulate the appetite out of proportion to its beneficial effects does not conform to our experience. If rapid alteration is indicated, the gonadotropins and testosterone, alone and in combination, have been used with success.[61] A similar type of functional obesity may develop after pregnancy or the menopause.

The second category includes the obese patient with a hypothalamic lesion due to trauma, inflammatory disease, vascular lesions or tumors at the base of the skull or midbrain.[53] The patient may appear similar to those with functional obesity, but in childhood he is usually smaller and has retarded bone development and stigmas of his particular cranial lesion. Treatment obviously consists in combating the etiologic factor, together with dietary and endocrine measures. In all cases of obesity, organic lesions must be carefully ruled out.

Anorexia Nervosa

Increasing attention has been given to anorexia nervosa in recent years.[62–64] Attempts to differentiate anorexia nervosa and Simmonds's disease have been difficult, since it is agreed generally that the starvation regimen of anorexia nervosa leads to a secondary hypopituitarism that ends with a clinical picture almost indistinguishable from that of Simmonds's disease.[65] However, recent work has shown that in anorexia nervosa, although the estrogens fall to a level analogous to that of childhood or Simmonds's disease, the urinary excretion of 17-ketosteroids is not markedly altered.[66] This appears to be an excellent differential technic to establish the diagnosis, since both components fall in Simmonds's disease.[67]

The basis of the therapeutic approach in anorexia nervosa is said to be psychiatric.[68] An analysis of the patient's background and personality, with therapeutic conferences and situational adjustments, may result in the resumption of proper eating. Close attention to the diet is essential, for only high-calorie food should be allowed, and it is occasionally advisable to insist that the patient eat more than is desired. When the appetite returns, the patient may eat astonishing amounts of food and weight gain is rapid, but recovery does not necessarily mean cure, for recurrences are not uncommon. In women, the menses may not return for several years. Younger patients are usually easier to treat, and the longer the illness the more guarded the prognosis. Intercurrent infections are dangerous.

The use of endocrine preparations is of questionable value. Thyroid appears to be detrimental by enhancing the emaciation and thus burning up more tissue. Insulin may be used to stimulate the appetite but, since insulin sensitivity may be pres-

ent, must be given cautiously. Pituitary extracts are ineffective. The use of vitamin supplements, although not specific, is of value.

The production of intermediate degrees of hypopituitarism, by temporary dieting, in people with labile endocrine systems is worthy of note. A patient who four years previously lost 40 pounds in four months by dieting, which she has since regained, but who has remained amenorrheic is a case in point.

Simmonds's Disease

Destructive lesions of the anterior pituitary gland, usually due to surgical procedures, trauma, tumors or granulomas, hemorrhage, diffuse fibrosis or post-partum necrosis, occasionally result in Simmonds's disease.[69] Necrosis of the anterior pituitary gland following a difficult puerperium with hemorrhage is the commonest etiology[70] of this very rare disease. In post-partum pituitary necrosis, the patient may die promptly, even if vigorously treated, or may develop a chronic hypopituitarism with a low basal metabolic rate, a low blood sugar, amenorrhea, anemia, loss of body hair, apathy, asthenia and precocious senility, and usually cachexia, although this is not an essential feature. Another pregnancy, if possible, permits pituitary regeneration, and the patient may become improved.[70]

Patients with Simmonds's disease run a variable course,[71] termination usually depending on the causative agent or an intercurrent infection, for even complete hypophysectomy is not necessarily fatal.[72] Most of the findings in hypopituitarism are related to atrophy of the endocrine organs maintained by the pituitary gland. Although it is obviously desirable to treat the cause of the pituitary destruction, substitutive therapy for the peripheral glands is usually the only course available. Although these may not be very successful, a program should be carefully worked out and varied for the needs of each patient. Anterior pituitary extract is of no great value, but favorable results have been reported with chorionic hormone.[73] Estrogens and androgens, used separately, may be of help. Adrenocortical insufficiency is often present, and a high-salt diet with desoxycorticosterone is used to combat this condition.[74] Although hypothyroidism exists, thyroid must be given cautiously, since it may accentuate an adrenocortical insufficiency.[75] Hypoglycemia occurs commonly,[76] and frequent feedings may be necessary.

Acromegaly

Acromegaly has a long and progressive course, with spontaneous remissions and exacerbations. Irradiation of the pituitary gland has received much favorable comment recently, and it is said that it produces relief of some of the troublesome symptoms, such as the severe headaches and eye changes, and some slowing in the progression of permanent changes and the occurrence of complications.[77, 78] Exacerbations may necessitate several courses of treatment, and the prognosis is always guarded.

Complications are common. Diabetes mellitus occurs in 17 per cent of the cases on an average of nine years after the onset of acromegaly.[79] Contrary to the usual statements, the diabetes is not more difficult to control than the usual type. Cardiac enlargement and failure develop with surprising frequency: in one series, 18 of 24 patients had heart failure.[80] The cause was not clear, but the abnormality responded to the usual treatment. It is well known that macrosplanchnia develops in acromegaly, but whether the heart enlarges because of a specific action of the pituitary gland or because of increased work is debatable, and this type of heart disease merits further study. Enlargement of the thyroid gland and elevation of the basal metabolic rate are common. This type of hyperthyroidism is unusual in that response to iodine is not spectacular, thyroid surgery is hazardous, and postoperatively the fall in basal metabolism is not marked.[81] However, if hyperthyroidism is a persistent symptom, subtotal thyroidectomy is advisable, since it may aid or prevent diabetes or heart failure. There have been no recent favorable reports on the use of sex hormones to inhibit pituitary activity in this disease.

Cushing's Disease

Great efforts to distinguish between Cushing's disease (pituitary basophilism) and hyperadrenocorticalism due to primary adrenal neoplasms or hyperplasia are proceeding.[82-84] Attempts to differentiate these two conditions have been rather uncertain because of the pleomorphic character of the syndromes and the intermediate pictures described.[85] This situation is due in large part to the striking differences attributable to the sex and the age of the patient at the onset of the disease. Cushing's disease is regarded as a primary basophilic adenoma of the pituitary gland, which probably exerts its effects by stimulating the adrenal cortex to produce excessive amounts and abnormal types of steroid hormones. This results, in the adult, in the frequently described picture of hirsutism, obesity, painful striae, hypertension, diabetes, osteoporosis, rubicundity and weakness. There is an absence of virilizing effects, and the 17-ketosteroid excretion in the urine is not markedly elevated; in young people bone development may be retarded. These findings may serve to distinguish Cushing's disease from primary hyperadrenocorticalism.

In general, the successes attending the irradiation of the pituitary gland in Cushing's disease

have been only rarely conspicuous. In a recent report from Albright's laboratory,[86] remarkable results have been obtained by the use of testosterone propionate. This was given in 25-mg. doses every other day, and the patients developed immediate nitrogen and phosphorus retention, urinary calcium output decreased, and there were gains in weight and strength. These findings were reversed when treatment was stopped or estrogens were administered. This appears to be a most promising type of treatment on theoretical and practical grounds, and merits extensive trial. In another report, the use of Stilbestrol was reported as beneficial.[87]

Gonadal Dysfunction

It is generally agreed that many gonadal dysfunctions are primarily of pituitary origin, yet it is not the pituitary but the steroid hormones that are being used extensively in these endocrine problems. It would be of extreme advantage, however, to have a more physiologic method of stimulating the ovaries, either to induce the normal sequence of events in the menstrual cycle or to act at a given point in the cycle, such as to induce follicle formation or to cause ovulation in the formed follicles or luteinization of the follicle cysts. The immense literature on this subject was recently reviewed,[88] but the conclusions regarding the pituitary hormones can be simply restated, since results are so discouraging or equivocal. Chorionic hormone alone is of no value.[24, 89] Pregnant-mare serum has been reported to induce ovulation, chiefly by intravenous administration,[90] but this must be a rare phenomenon.[91–93] Purified pituitary gonadotropic substances are just coming into use. It is quite obvious that women do not respond to these substances in a way analogous to the reactions of laboratory animals.

The ovaries of a large group of patients after the injection of various gonadotropic substances, alone and in combination, were studied.[94] The results were variable, and the desired effect was rarely obtained. Ovulation is a delicately controlled mechanism, resulting only from the appropriate balance of hormones present at the propitious moment. The dosage, time, duration, sequence and route of administration and proper combination of hormones must be observed. It is also quite obvious that diseased ovaries will not respond to the same stimulus as normal ones. Attempts to strike the necessary balance are crude as yet, but two therapeutic approaches are suggested. The use of the chorionic hormone in combination with the pituitary synergic principle has been successful in inducing ovulation.[23, 95, 96] The sequential use of pregnant-mare serum (400 to 800 international units daily) for the first ten days of the menstrual cycle, followed by chorionic hormone (500 to 750 international units daily) for the next ten days, is reported to have given a progestational endometrium in 15 of 29 cases.[97] These combined treatments seem worthy of trial in anovulatory cycles. The administration of small stimulating doses of estrogens in combination with the gonadotropins is believed to increase their effectiveness.[88]

Cryptorchidism

The usefulness of the gonadotropic hormones in the treatment of undescended testes has been clearly defined.[98, 99] It is effective only in cases in which no mechanical obstruction to descent exists, and these testes would probably descend at puberty of their own accord. However, in cryptorchidism, a trial with the chorionic hormone is advisable, since the testes may come down, and if not, they are enlarged so that surgery is facilitated. Pseudocryptorchidism must be carefully ruled out. The testes that are lower in the inguinal canal are the likeliest to respond to therapy.

There is some disagreement concerning whether treatment should be started just before puberty or in childhood. The tendency is to start at an early age, since premature closure of the epiphyses or enlargement of the genitalia is not a likely complication of the therapy.[100] The usual course of treatment is 100 to 500 international units of chorionic hormone three to six times weekly for eight or nine weeks. About 20 to 25 per cent of the cases are benefited; the rest should then be treated surgically. The administration of 5 to 10 mg. of testosterone propionate along with the chorionic hormone is said to give improvement in cases in which each hormone has failed when given separately.[101] The disadvantages of using testosterone in children must be considered.

Diabetes Mellitus

The interest in the role of the pituitary gland in diabetes received considerable impetus from Young's discovery that chronic diabetes could be induced in dogs by long-continued injections of anterior pituitary extracts.[102] Insulin, if given along with this extract, or shortly afterward, prevents or cures the diabetes. If the diabetes has existed for several months, insulin has no curative effect. From this was evolved the principle that the pancreas is susceptible to complete exhaustion, but if rested early, it can be revived. It has therefore been suggested that human diabetes be treated early and intensively with a low-carbohydrate, low-calorie diet and insulin, under conditions that tend to rest the pancreas.[103]

The significance of the pituitary gland in the usual type of human diabetes is uncertain. In the hyperpituitarism of acromegaly, it is a late and not

an extremely frequent complication.[79] Although favorable results have been reported,[104] in general the use of estrogens in the treatment of diabetes by suppressing pituitary function has been discouraging.[105, 106] These recent findings, however, have proved most stimulating, and further study is needed of the relation of the pituitary gland to human diabetes.

Hyperthyroidism

With the well-recognized dependence of the normal thyroid gland on the thyrotropic hormone of the pituitary gland, attempts have been made to attribute Graves's disease to pituitary overactivity. The hyperthyroidism of acromegaly may be on this basis, but there is no satisfactory evidence that the usual case of Graves's disease has a similar etiology. Occasional and inconstant successes in the treatment of hyperthyroidism have been reported by the use of estrogenic substances[107] and chorionic hormone.[108] These studies, as representing a medical approach to the treatment of hyperthyroidism, are interesting but of no general therapeutic moment as yet.

An unusual subgroup of Graves's disease, referred to as "malignant exophthalmos," is being stressed by Means and his group.[109] In these patients, the exophthalmos is profound, although the basal metabolic rate is only slightly elevated, if at all. This exophthalmos is probably due to large excesses of thyrotropic hormone, which is reported to cause a specific hypertrophy, edema and lymphocytic infiltration of the extraocular muscles.[110] This condition must be carefully differentiated from ordinary exophthalmic goiter, since in the former, thyroidectomy may prove disastrous by increasing the exophthalmos until blindness results. The appropriate treatment, therefore, in the selected case is to attempt to suppress the pituitary overactivity. This consists in the use of iodides and thyroid in a balanced combination to depress the basal metabolic rate and to inhibit pituitary activity. Estrogens are worth trying. If the exophthalmos progresses, x-ray treatment to the pituitary gland and to the orbit may help,[111] and as a last resort, if vision is menaced, orbital decompression may be indicated. If the hyperthyroidism requires treatment, x-ray therapy to the thyroid gland is preferred. Surgery, if used, requires the most considered preoperative and postoperative care.

* * *

To summarize this mass of new work is difficult. It may be stated, however, that the importance of the pituitary gland is fairly well established in many abnormalities of the endocrine glands. Even though it may frequently be the primary factor, the use of pituitary hormones has, on the whole, been disappointing in therapeutic effects. This is due to the difficulties in obtaining adequate sources and in purification. It is also unwise to use continuous therapy because of the temporary immunity produced by injected pituitary hormones, so that intermittent therapy is imposed. As a result, pituitary deficiencies are now more effectively treated by the use of endocrine hormones derived from the peripheral glands.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 28191

PRESENTATION OF CASE

A fifty-four-year-old Italian housewife was admitted to the hospital because of pain in the right shoulder blade.

The patient was in good health until seven months before entry, when she began to lose weight and developed a dull aching pain in the area of the right shoulder blade. The pain was not related to meals, exertion, posture or time of day. It varied greatly in intensity, sometimes remitting completely. At times, it radiated down the right arm to the hand, and on other occasions it extended to the left shoulder blade. Throughout the illness, there were transient periods of low fever, with occasional chills and night sweats. At times, there was a slight cough. Strength and weight were progressively lost, the latter to the extent of 27 pounds during the illness. Nine months before entry, the menses (previously regular) ceased. Slight nasal bleeding occurred at the times of some of the expected periods. The appetite became poor early in the illness. Gaseous eructations, unaccompanied by nausea or vomiting, frequently followed meals. Concomitantly, the patient's previous bowel regularity was replaced by alternating bouts of constipation and diarrhea. Borborygmi and griping lower abdominal pains accompanied the constipation, whereas the alternating periods of four or five watery stools a day were painless.

The patient had worked in a chocolate factory until four years before entry. She was accustomed to a glass of wine with meals. The past and family histories were irrelevant.

On admission, the patient appeared fairly well developed, but emaciated, seeming ten years past the stated age. The skin was sallow, and the mucous membranes were pale. The pupils were small and slightly irregular. The fundi showed arteriosclerotic changes. The tonsils were large and cryptic. A few pea-sized lymph nodes lay in the right anterior part of the neck. The breasts were atrophic. There were dullness and diminished tactile fremitus and breath sounds over the left upper lobe of the lung, anteromedially. The heart sounds were loud over this area. Posteriorly, over the right upper lobe, there was impaired resonance, with diminished tactile fremitus, breath sounds and voice sounds. The left border of the heart was displaced 2 cm. beyond the midclavicular line; the pulmonic second sound was greater than the aortic, and the mitral first sound was loud. A systolic murmur was loudest over the pulmonary area, but could be heard well out in the axilla. The abdomen was flat and soft. A large, firm mass consistent with liver and moving with respirations extended 9 cm. below the costal margin. Traube's space was diminished. The spleen was not palpable. Vaginal and rectal examination showed the cervix displaced to the left, and the uterus fixed in retroversion. The pelvic contents seemed "bound down," and there was some question of a polypoid mass high in the rectum. The pulse was of Corrigan type, regular at 95, and faint pistol-shot sounds were audible over the femoral arteries.

The respirations were 20, and the temperature was 99.5°F. The blood pressure was 130 systolic, 55 diastolic.

Examination of the blood showed a red-cell count of 3,200,000 with 7.5 gm. hemoglobin, and a white-cell count of 15,800 with 84 per cent polymorphonuclears, 11 per cent lymphocytes and 5 per cent monocytes. The van den Bergh reaction was normal. The serum albumin was 3.7 gm. and the globulin 2.7 gm. per 100 cc. The nonprotein nitrogen was 20 mg. per 100 cc. A bromsulfalein test showed 15 per cent retention of the dye. The urine showed a ++ test for albumin, with 80 to 100 white cells, a few red blood cells and many bacteria per high-power field in the sediment. Urine culture yielded colon bacilli.

An electrocardiogram was within normal limits.

Roentgenograms of the chest showed a mass measuring 12 by 11 by 10 cm. in the posterior portion of the right upper lobe, displacing the trachea to the left (Fig. 1). The intercostal spaces in the region of the mass were slightly wider than those on the left side. Multiple round shadows were spread throughout the remainder of both lung fields. There was destruction of the medial end of the twelfth left rib. The liver shadow was large.

No therapy was instituted. The temperature gradually fell to 97°F., and the patient failed progressively. Death occurred on the tenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. LOWREY F. DAVENPORT: We are given enough evidence to say that this patient definitely had a malignant tumor. The crux of our problem is to decide where the tumor originated, whether the tumor mass seen in the x-ray film was primary in the lung or metastatic from some other focus.

May we see the films?

DR. AUBREY O. HAMPTON: In addition to the area of destruction described in the record, the pa-

tient had a pathologic fracture of the fourth lumbar vertebra, probably due to the same process. These round "snowballs" in the chest are a little unusual in primary cancer of the lung, but this huge mass occupying the upper lobe is unusual in metastatic cancer, so that we have a fifty-fifty tossup.

DR. DAVENPORT: Let us take up first the question of primary cancer of the lung. I believe that the one diagnosis of primary carcinoma of the lung will not adequately explain all the symptoms or the laboratory data. The immediate cause for entry into the hospital was pain, most severe in the region of the right shoulder but also involving the left shoulder. It is a little disturbing if we assume that all this was metastatic disease in the lungs, that the patient began to have pain from metastasis so early. But, about the same time that she felt the pain, she was also having some epigastric symptoms. The appetite failed very early in the disease, and she had gaseous eructations unaccompanied by nausea and vomiting. About the same time, she began to have very definite bowel symptoms — alternating periods of constipation and diarrhea. In the average case of primary lung cancer, fever is satisfactorily explained only if a bronchus is obstructed and suppuration develops behind the block. There are periodic elevations of temperature, usually followed, if the temperature falls, by unblocking and expectoration of large quantities of foul material. Although we are told that the patient had a slight cough at times during the illness, that was certainly not a major symptom. At no time did she raise blood, and whereas that in itself does not exclude a primary lesion in the lung, it is definitely against it. We have seen bleeding in cancer of the lung very commonly and in metastatic cancer very rarely. It would be possible to explain part of the abdominal symptoms on the assumption that the primary process was in the lung. We are given definite evidence that the liver was enlarged, and we do

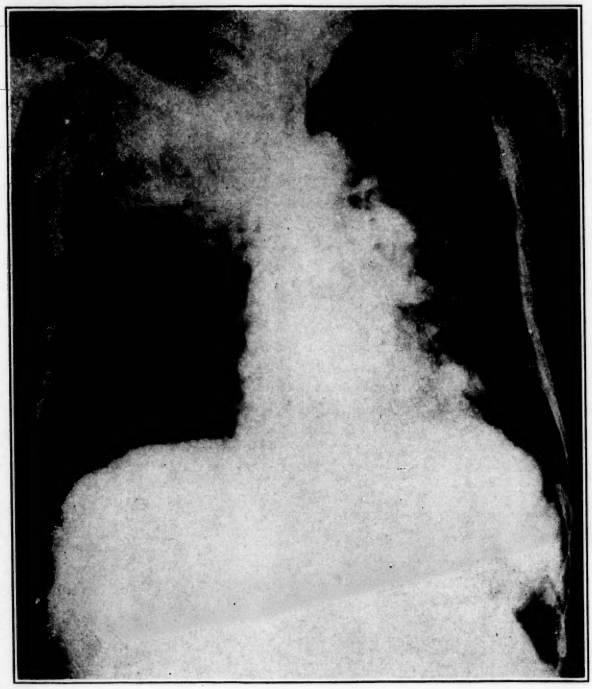

FIGURE 1.

know that cancer of the lung frequently metastasizes to the liver and to the bone; however, it is most unusual for metastases to explain these very marked and dramatic bowel symptoms that the patient had from the beginning of the illness.

I believe the origin of this cancer was outside the lung. We have evidence enough to warrant discussing three other situations where it might have been primary. The patient had a definitely enlarged liver. Rectal examination showed a questionable polypoid mass, and one urine specimen gave evidence of kidney infection, with a few red blood cells.

Could this have been a kidney tumor? We know that hypernephroma metastasizes very frequently to the lungs and gives large metastases. This is not the typical picture of the so-called "cannon-ball metastases" that we have seen on several occasions. We have little evidence to go on. We have no kidney symptoms during these seven months, and the only data on the kidney were obtained in a terminal phase of the illness, so that I believe it is fair to assume that the kidney findings were primarily on the basis of infection. We are told very definitely that she had colon bacilli in the urinary tract toward the end.

Could this have been a primary tumor in the pelvis? In a patient of this age, one must suspect the female organs as being the possible source of the lesion. However, she had a careful pelvic examination. She had no story of abnormal bleeding. Cancer, both in the cervix and in the uterus, spreads most commonly by direct extension, and although remote involvement of the lungs does occur, one would expect much more evidence of involvement of the pelvic organs than is given on this examination.

A great deal of the evidence points toward the liver as the primary source of the cancer. We are told in the history that the patient was accustomed to drink a glass of wine with her meals. That in itself in an Italian woman of this age would not be of any particular significance. However, the laboratory data show that the liver function had been very definitely impaired. We are told that the patient had a serum albumin of 3.7 gm. and a globulin of 2.7 gm. per 100 cc., making the total protein definitely low, and the albumin-globulin ratio, although not reversed, is definitely lower than the accepted normal. That, in the absence of definite kidney disease, is fairly good evidence that there was some difficulty with the manufacture of proteins in the liver. We know that low serum proteins can result from starvation and also from a generalized and diffuse liver disease. We are also given the information that the bromsulfalein test showed 15 per cent retention of dye, and if we accept the ordinary figure that a normal liver shows less than 5 per cent retention, we must assume again that there is definite evidence of liver damage. It is also generally accepted that extensive metastatic involvement of the liver can be present without impairment of liver function. Physical examination showed that Traube's space was smaller than usual. That is a poor diagnostic sign, a diminution of the tympany that ordinarily occurs with a stomach containing air. It may be diminished with a large liver but also may be diminished in patients with stomachs in which very little air is present. I should therefore assume, from the very mention of such a poor diagnostic sign as Traube's, that the liver was markedly enlarged, not only by palpation but definitely, to the left, by percussion.

If we focus our attention on the liver and assume that the patient had liver disease, what are the chances that this was a primary cancer in the liver? Cancer of the liver is rare statistically, much rarer than cancer in the lung or bowel or other foci that we have been discussing. Nevertheless, it does occur often enough to warrant our considering it seriously in this case. It is generally stated that cancer occurs in a liver that is already damaged, and we have only laboratory data to point to liver insufficiency. The absence of ascites and jaundice is a little bit disturbing but does not necessarily rule out cirrhosis. If, then, we assume that the patient had some liver damage and that she developed cancer of the liver on a cirrhotic background, can we explain most of the symptomatology? I think we can, and to me it is the only way in which I can make one diagnosis that will explain all the symptoms. In cirrhosis of the liver, one of the early signs is disturbance of digestion, and nausea was one of the early symptoms in this case. Later, because of the disturbance of liver function and secondary disturbance of the digestion in the bowel, symptoms such as we have here of alternating diarrhea and constipation may occur.

Is there any way in which we can deduce primary cancer in the gastrointestinal tract? There is not enough evidence to implicate the stomach. There was no bleeding. We have not been told anything about a stool examination. But I assume that bleeding could not have been an important symptom.

Dr. Tracy B. Mallory: There were three guaiac-negative stools.

Dr. Davenport: That is of some help.

Cancer in the lower bowel ordinarily does not metastasize so widely, metastasizing usually by direct extension through the lymphatics. Particularly in the rectum, epidermoid carcinoma rarely invades the blood stream. Is it not a good general

rule that epidermoid cancer invades the lymphatics, but not the blood stream?

DR. MALLORY: Yes; I think that is probably so.

DR. DAVENPORT: I shall make as my diagnosis a primary malignant tumor in the liver, probably developing on a cirrhotic background, with metastases to the lungs and with inflammation in the pelvis binding down the uterus and involving the lower gastrointestinal tract, which may or may not have been a part of the terminal picture. The transient bouts of fever and the occasional chills and night sweats go well with infection in the liver, but could occur with tumor and may have been partly due to breakdown of a tumor mass in the liver.

DR. MALLORY: Dr. Hampton, have you any further comment?

DR. HAMPTON: As one looks at the chest films, one can see that the spleen is not enlarged, and according to Dr. Richard Schatzki,* primary carcinoma of the liver is commonly associated with advanced cirrhosis. The cases that he reported had large spleens, and varices in the esophagus. I wonder how we can explain the absence of enlargement of the spleen.

DR. EDWARD F. BLAND: Someone might wonder what I had to do with this case, but it so happens that I was visiting on the medical ward for Dr. J. H. Means, who was away. Dr. W. M. Jeffries, the senior house officer, and I took this case up in some detail, and we reasoned somewhat as Dr. Davenport did, but did not go quite so far in regard to the liver. The patient was too sick to have many special diagnostic procedures performed. The X-ray Department strongly implied that they thought this was a primary malignant lesion of the lung. We were inclined to metastatic involvement of the lungs because of the preceding gastrointestinal symptoms. I think our final diagnosis was metastatic carcinoma of the lungs, liver and bones from an undetermined focus, but probably in the gastrointestinal tract. Those of us who palpated the abdominal mass believed it to be liver with metastatic involvement.

DR. DAVENPORT: What did you think of the polyp in the rectum?

DR. BLAND: We could not identify it.

DR. F. DENNETTE ADAMS: Did anyone give thought to the pancreas?

DR. BLAND: We did not.

DR. ADAMS: The woman had diarrhea, loss of weight and digestive symptoms.

DR. HAMPTON: We have not seen metastases to the lung from either pancreas or liver with that appearance. I vote against the liver or pancreas.

*Schatzki, R. Roentgenological diagnosis of primary carcinoma of the liver. *Am. J. Roentgenol.* 46:476-483, 1941.

A PHYSICIAN: I believe that the rectum was involved.

DR. DONALD S. KING: I should guess that the primary site was the lungs. We have one case—there is always one!—with metastasis to the contralateral lung. I do not quite see why metastases to the liver and bones and so forth, would not account for all the symptoms. I grant that it is an unusual x-ray picture.

DR. MALLORY: It is difficult to explain metastasis to the contralateral lung from bronchiogenic cancer, but such metastasis has occurred. I think it usually results from involvement of the hilar node and extension from there into the pulmonary artery, which permits seeding of the opposite lung. We occasionally see tuberculosis spread by that method, and it is possible with cancer but certainly unusual.

DR. FLETCHER H. COLBY: It still could be a lesion of the kidney. The unusual thing is the massive tumor mass, but I should still say that the patient could have had a renal-cell carcinoma.

DR. HAMPTON: That is a possibility, but the films do not look right. Lymphoma is the next thing we should consider, I think.

DR. MALLORY: Have you ever seen nodules as discrete as that with lymphoma in the lung?

DR. HAMPTON: Once; but not so many and perhaps not quite so smooth and sharp.

DR. DAVENPORT: Is it not true that one can have a tremendous tumor mass in the liver, and no demonstrable change in liver function?

DR. MALLORY: Yes; with metastatic, but not with primary, carcinoma.

DR. HAMPTON: What do you think of the absence of enlargement of the spleen?

DR. WILLIAM B. BREED: I think it depends entirely on the stage of advance of the cirrhosis.

DR. MALLORY: One can say that symptoms occur only in advanced cirrhosis.

DR. BREED: Then that is the answer to it. The patient should have had an enlarged spleen.

DR. MALLORY: I think Dr. Hampton has a strong point there.

DR. BREED: So do I.

CLINICAL DIAGNOSIS

Carcinoma of lung (? bronchiogenic), with metastases to lungs and liver.

DR. DAVENPORT'S DIAGNOSIS

Carcinoma of liver, with metastases to lungs.

ANATOMICAL DIAGNOSES

Carcinoma of right kidney, with metastases to lungs, bronchial lymph nodes, vertebral bone marrow and left twelfth rib.
Nephritis, suppurative, left, acute.
Cystitis, diphtheritic, urinary bladder, acute.
Emaciation, marked.
Brown atrophy of organs.
Leiomyomas of uterus.
Arteriosclerosis, minimal of aorta.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Post-mortem examination showed that the primary tumor was a hypernephroma. The right kidney was nearly twice the normal size, and the liver was small — 1600 gm. — and entirely normal. The lungs were studded with metastases; one extremely large one in the right upper lobe was immediately subpleural on the posterior surface of the lung and did not connect with any bronchus. One of the smaller metastases had invaded a bronchus and started to grow as a plug of tumor tissue up the bronchus, so that as a matter of fact if the patient had been bronchoscoped a biopsy would have proved the diagnosis without any question.

DR. HAMPTON: Which bronchus?

DR. MALLORY: It was the main bronchus of the left upper lobe.

DR. HAMPTON: I wondered about that. This wedge-shaped shadow in the left upper lobe bothered me, but I did not mention it. There is some atelectasis in that area.

DR. BLAND: I might say that the edge of the liver was 9 cm. below the costal margin, but the patient was emaciated.

DR. RICHARD CLARKE: At the time of post-mortem examination, was the liver down, or was it up at the costal margin?

DR. MALLORY: It was 2 cm. below the costal margin.

A PHYSICIAN: Can the kidney rotate the liver downward?

DR. MALLORY: I think it was the kidney that was felt. It was the right kidney that contained the tumor, and I can remember a kidney that I mistook for liver once.

DR. DAVENPORT: Only one thing bothers me. Why was the liver function so depressed?

DR. ALFRED KRANES: The only evidence of depression was the 15 per cent dye retention. The test is not extremely reliable.

DR. MALLORY: There was a somewhat low serum protein. On the other hand, the patient had a severe pyelonephritis on the other side. The right kidney was almost completely replaced by tumor, and the left kidney showed an active pyelonephritis. Accordingly, I think the kidneys could have been responsible for the low serum protein.

A PHYSICIAN: Was there a tumor in the rectum?

DR. MALLORY: There was a fibroid on the posterior surface of the uterus.

DR. COLBY: Was there anything else in the pelvis?

DR. MALLORY: Nothing.

CASE 28192

PRESENTATION OF CASE

First admission. A twenty-nine-year-old electric welder was admitted to the hospital because of recurrent masses in the groin.

Fifteen years before entry, the patient first noticed a swelling in the right groin. Ten years later, because of enlargement of this mass, a biopsy was taken in a community hospital and reported as "lymphoblastoma." Subsequently, the patient was given roentgen-ray treatments to each groin about once a year. Except for occasional slight pain over the right upper leg anteriorly, persistent swelling in the right groin remained the sole symptom until six weeks before entry, when occasional severe gnawing pain unrelated to meals appeared in the upper abdomen and radiated down to the pubis. During intervals between the attacks of pain, the abdomen was frequently sore. Concomitantly, the patient began to feel listless and tired, and lost about 7 pounds of weight. A few days before entry, he had several chills, accompanied by a fever of 104°F. The lump in the right groin showed no recent swelling, and the patient was not aware of any other masses.

The past and family histories were irrelevant.

On admission, the patient appeared well developed and nourished, with a warm dry skin. The throat was somewhat reddened. A few rather small lymph nodes were palpable in the front of the neck on each side, and a few similar nodes were felt in each groin. The heart and lungs were normal. The abdomen was tense and firm, without definite tenderness. The liver and spleen were not palpable. The extremities were normal.

The blood pressure was 115 systolic, 80 diastolic. The temperature was 101.5°F., the pulse 90 and the respirations 22.

Examination of the blood showed a white-cell count of 7400 with 69 per cent polymorphonuclears, 4 per cent large lymphocytes, 14 per cent small lymphocytes and 13 per cent monocytes. A second examination showed a white-cell count of 6900, including 73 per cent polymorphonuclears, 2 per cent small lymphocytes, 23 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils. The hemoglobin varied from 14.5 to 12.4 gm. The blood Hinton reaction was negative. Agglutination tests with typhoid and brucellar antigens were

negative. A blood culture was negative. The urine and stools were normal.

Roentgenograms of the gastrointestinal tract showed a normal esophagus and stomach. There was some delay of barium in the second portion of the duodenum, and deformity of the third portion due to pressure of an ill-defined extrinsic mass. The mucosa appeared uninvolved. The lower border of the liver was rather low, but the spleen was not definitely enlarged. A roentgenogram of the chest showed no evidence of disease.

Roentgen irradiation was given for five days, in total dosage of 600 r to the right groin and 100 r to the anterior liver field, followed in six days by a course of 1200 r to the posterior lumbar region. Two days after this treatment was begun, the temperature rose to 104°F., and it ranged from 101 to 104°F. for the next two weeks. Diarrhea likewise appeared, with seven or eight soft movements a day. The patient was discharged on the twentieth hospital day.

Final admission (eighteen days later). The patient remained at home in bed. The temperature continued high, and he experienced occasional chills. He felt quite weak, and the diarrhea gradually subsided.

On re-entry, physical examination was essentially as before. Areas of first-degree roentgen dermatitis appeared over the epigastrium and lumbar spine.

Laboratory studies, including three negative blood cultures, were essentially as before, with the addition of a normal lumbar puncture, a negative stool culture, and a tuberculin reaction that was weakly positive in a dilution of 1:50,000.

A roentgenogram of the chest showed generalized miliary lesions, involving both lungs entirely, and seeming most like miliary tubercles. There was no evidence of pleural fluid, or of enlargement of hilar or mediastinal lymph nodes. A questionable area of localized infiltration 1.5 cm. in diameter lay in the right apex.

In the course of a month, the patient had remittent fever, the temperature varying from 101 to 104°F. and spiking each afternoon. The pulse was correspondingly high. Roentgen therapy was given to the lung fields in doses of 600 r to the left and 750 r to the right. Subsequent roentgenograms taken four and twelve days after this first examination showed a slight increase in the miliary lesions, and no change thereafter. In the second and third weeks in the hospital, abdominal fluid began to accumulate. Paracentesis yielded 2500 cc. of turbid green sterile fluid with a specific gravity of 1.010. The centrifugate showed only acute inflammatory cells, with no evident organisms or tumor cells. The patient continued to fail rapidly, dying on the thirty-first hospital day.

Differential Diagnosis

Dr. Myles P. Baker: On the first admission, the diagnostic problem was that of a patient with upper abdominal pain present for six weeks, associated with fatigue, chills and fever. The locus of the pain appears to have been just above the umbilicus, probably in the midline, and it was crampy, pointing to something associated with the small intestine. There were several important features of the physical examination at the time of this admission. The first was the absence of generalized lymphadenopathy. I take it from the description that there was no massive swelling in either groin and that no large mass had been present for many years. Since x-ray examination of the chest was negative, we have no proof or evidence of mediastinal lymph-node enlargement, and there was no enlargement of the spleen. Moreover, there was x-ray evidence of an extrinsic mass, pressing on the third part of the duodenum, which might well have contributed to the upper abdominal crampy pain that had been one of his chief complaints. Finally, there was a distinctly unsatisfactory reaction to what was presumably adequate radiation therapy for a lymphomatous disorder. The blood picture is emphasized here. I can only say that the increase in monocytes is interesting but not necessarily associated with tubercle formation. It is obvious that those responsible for this man's care hoped that he had a radiosensitive lymphoma and treated him accordingly. They must have been dissatisfied with the effect of the treatment and discharged him with a distinctly poor prognosis and, I should think, with considerable doubt that the previous biopsy diagnosis of lymphoblastoma had been correct.

Against the diagnosis of lymphoma is the clinical course. It must be rare to have lymphoma localized in the groin for fifteen years — from the age of fourteen to twenty-nine. We did not know from the story whether the x-ray treatment approximately once a year effected any demonstrable decrease in the size of this solitary swelling. Presumably, it did, but there is no evidence to that effect. Lymphoma in a boy in his teens or early twenties is apt to progress without long remissions, and since this man had rather scanty treatment, I think the duration is distinctly against the diagnosis and brings up the question whether this could have been tuberculous adenitis from the start.

On the second admission, the patient returned with the same fever, in addition to positive x-ray findings in the chest, only three or four weeks after the previous negative chest plates. On this admission, along with the negative blood cultures and negative lumbar puncture, he had a weakly

positive tuberculin reaction to a relatively high dilution of tuberculin.

I should like to ask Dr. Hampton to comment on the chest x-ray films.

DR. AUBREY O. HAMPTON: This series of films extends over a period of a year and seven months, and for the first seventeen months the chest was normal. At the time of entry into the hospital with fever, it shows this miliary process in the lung: a very fine, diffuse, symmetrical process, without anything else — no enlargement of the lymph-nodes, no areas of consolidation, no fluid and no areas of calcification. After the x-ray treatment, it appears that the chest is no better, and the miliary lesions are larger. Examination of the spine, which was done on the outside, is not reported. In our films, the body of the fifth lumbar vertebra is uniformly dense. One can see bone trabeculae in it, and if the patient were not so young, I should have to say that he had Paget's disease. It is true, however, that lymphoma produces new-bone formation in bones that appears somewhat like that, particularly if it has been treated.

The pressure defect in the duodenum is not very obvious in this film. It must have been more obvious to the man who fluoroscoped the patient; at any rate, there is some spasm and delay in the third portion of the duodenum as it crosses the spine. The liver shadow is rather faint in the lower portion and not very large. The spleen does not appear to be very enlarged. The hands and feet were examined, I suppose, to discover sarcoid; no abnormalities are present.

DR. BAKER: What about the interpretation of the right apex during the second admission?

DR. HAMPTON: I cannot be absolutely sure that the apexes are not similar to the rest of the lung. Certainly, there was nothing in the apex two months before.

DR. BAKER: Could you rule out metastatic carcinoma on the basis of the x-ray films on the second admission?

DR. HAMPTON: I think we have seen one case in this hospital with a fine miliary process said to be metastatic carcinoma.

DR. DONALD S. KING: Even that case is unproved.

DR. BAKER: The question comes up, What lesions can produce this kind of miliary process in the lungs? First of all, the likeliest is tuberculosis. With such a diagnosis, I think the weakly positive skin tuberculin test is consistent in a sick person.

DR. ALLEN G. BRAILEY: The dilution was 1:50,000.

DR. BAKER: I beg your pardon. Then we shall have to say that the strongly positive tuberculin test is going to be somewhat difficult to explain in such a sick person.

Lymphoma has been reported as giving an x-ray picture that is difficult to distinguish from miliary tuberculosis. If lymphoma affects the lung parenchyma, it is much more likely to do so in the form of peribronchial infiltration or as an isolated nodule. It may be the site of cavity formation or it may take the form of pneumonia with or without atelectasis, but this would be a distinctly rare x-ray picture with lymphoma.

The other possibilities can be ruled out on the clinical story alone, such as silicosis, which usually gives coarser mottling than this. Yeast infections run a more benign course, and do not give the picture of such an acutely sick patient. One or two patients that I have seen with sarcoid, in whom the x-ray picture was consistent with miliary tuberculosis, have been in much better health than this man was. I have followed one daily over a course of five years, and at no time was she at all ill; she was always ambulatory, had no symptoms except those referred to her iritis, and now, five years after the onset of the iritis, her chest is almost entirely clear. This is not true of the case under discussion. We are dealing with a man who was in his last month of life at the time when he developed this picture of miliary seeding. I think we can rule out a relatively benign process such as sarcoid on that basis. We have, as Dr. Hampton said, little reason to suspect metastasis to the lungs from a retroperitoneal mass such as sarcoma.

Could this man have developed miliary tuberculosis with a positive x-ray plate only six weeks after his film had been negative? That is possible, and although I cannot cite a definite case to back me up, I think that the likeliest diagnosis here is not lymphoma but tuberculous adenitis, with retroperitoneal tuberculous lymph nodes and acute hematogenous spread of infection, with a picture of miliary tuberculosis at the end, and tuberculous peritonitis. The accumulation of ascitic fluid with a low specific gravity is not diagnostic and could occur in lymphoma as well as in tuberculosis; I should be inclined, however, to dismiss the tuberculin test on the basis of the clinical story and x-ray findings and make a diagnosis of generalized tuberculosis as the most likely explanation for this man's signs.

A PHYSICIAN: What is the effect of radiation on tuberculous adenitis?

DR. HAMPTON: It was used for many years in the treatment with a dosage such as this patient had. I suppose the majority of people who treated such patients believed they improved. Much larger doses were given to active tuberculosis in the lung,

with the hope of fibrosing the process, and some workers have said that it improved active tuberculosis of the lung. I have done this accidentally, without any known effect. We had no hesitancy in treating this patient, even though our own first diagnosis was miliary tuberculosis, because if he had it, he had no hope of living, and if he had lymphoma we might put off death for a while. We gave a dose that we thought was safe even if he had miliary tuberculosis and could survive.

A PHYSICIAN: Does lymphoma never give a picture like this?

DR. HAMPTON: In the X-ray Department, we had quite a discussion about this case. In all the follow-ups on lymphoma, we have not seen a single example of a miliary process similar to this. We have had cases showing numerous nodules from 1 to 5 cm. in diameter but not a miliary process. We all admitted that some day we shall probably see one; there is no reason to suppose that we shall not.

A PHYSICIAN: Would this picture be consistent with septic infarcts?

DR. HAMPTON: I do not believe so.

CLINICAL DIAGNOSES

Diffuse lymphoma.
Miliary tuberculosis?

DR. BAKER'S DIAGNOSIS

Miliary tuberculosis, generalized.

ANATOMICAL DIAGNOSES

Miliary tuberculosis, generalized.
Tuberculous ulceration of duodenum, with perforation.
Tuberculosis of retroperitoneal lymph nodes.
Tuberculous enteritis, moderate.
Thrombosis of left adrenal vein.
Interadherence of aortic cusps, probably congenital.
Pulmonary edema, moderate, bilateral.
Tuberculous meningitis.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: Post-mortem examination showed very voluminous lungs, densely seeded, from top to bottom on both sides, with miliary tubercles; some nodules were considerably larger than miliary tubercles, reaching 1 cm. in diameter. There was a slight tuberculous peritonitis. The duodenum was unusual. A large ulcer was found beyond the papilla in the third portion, where the duodenum crosses the vertebral column. We had never seen a peptic ulcer beyond the papilla of Vater, and later examination showed that the walls of this ulcer were caseous and it was purely tuberculous in origin. It communicated with a retroperitoneal abscess cavity, and whether the tuberculosis was primary in the duodenum, spreading through the intestinal wall, or a tuberculous retroperitoneal lymph node spread in the reverse direction into the duodenum, we cannot say. There were multiple tuberculous ulcers in the colon, several isolated tubercles in the meninges over the cerebellum and very early diffuse terminal tuberculous meningitis. There were peculiar lesions in the kidney and heart that did not look like tubercles but like septic abscesses, each about 1 cm. in diameter and filled with green purulent material, which grossly did not remotely suggest caseation, but later examination proved that these were also pure tuberculous abscesses. I have never seen a case of tuberculosis in which tubercle bacilli were so numerous. They even showed up in great numbers in the sections stained with eosin and methylene blue.

DR. HAMPTON: I think we can trace the origin of this process on the x-ray films. The gastrointestinal examination was done two months before death. At that time, the patient had this indefinite outline of the third portion of the duodenum, with an extrinsic mass and normal lung. One can assume that tuberculous adenitis was primary because the mucosa of the duodenum is not grossly abnormal and no definite ulcer is seen.

A PHYSICIAN: Was the mass in the groin tuberculous?

DR. MALLORY: A small caseous nodule 1 cm. in diameter was found there. There was no evidence of lymphoma.

DR. BAKER: Were there any sputum examinations for tubercle bacilli on the second admission?

DR. MALLORY: No.

A PHYSICIAN: Would you doubt now the diagnosis of lymphoblastoma on the previous biopsy?

DR. MALLORY: Completely.

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PROCUREMENT AND ASSIGNMENT SERVICE

The mailing of the enrollment forms and questionnaires for the Procurement and Assignment Service was completed on April 24, and by now, every registered physician in the United States should have received them. These forms should be carefully filled out and IMMEDIATELY returned. If any physician has failed to receive the forms, he should write for them directly to the National Roster of Scientific and Specialized Personnel, 916 G Street, N. W., Washington, D. C.

ANNUAL MEETING

The one hundred and sixty-first anniversary of the Massachusetts Medical Society will be held at the Hotel Statler. The program of the meeting, which will be held on Monday, Tuesday and Wednesday, May 25, 26 and 27, appears elsewhere in this issue of the *Journal*.

The outstanding change in the usual sequence of events is one designed to permit all fellows of the Society to enjoy the scientific meetings more thoroughly than they have in the past; hence, the annual meetings of the supervising censors and Council will be held in the late afternoon and evening, respectively, of Monday, May 25, the day before the opening of the scientific sessions and the annual meeting of the Society.

The scientific papers to be presented at the four general sessions are largely concerned with War Medicine, that is, the application of medical science to war and its associated activities. Addresses by Dr. Frank H. Lahey, president of the American Medical Association, Dr. Morris Fishbein, editor of the *Journal of the American Medical Association*, Drs. Raymond A. Vonderlehr and Rolla E. Dyer, of the United States Public Health Service, and Mr. John M. Pratt, executive administrator of the National Physicians' Committee for Extension of Medical Services should be of particular interest. The Annual Oration will follow the annual meeting of the Society, to be held at eleven in the morning on Tuesday, May 26; the orator is Dr. William B. Castle, and his subject "Some Remarks on Therapy for Anemia." Following the annual dinner that evening, at which the guest speakers are Drs. Lahey and Fishbein, the Shattuck Lecture, "Medicine and Air Supremacy," will be given by Dr. John F. Fulton, of New Haven, Connecticut. The combined luncheons and meetings of the sections will be held on Wednesday noon, May 27, and extremely interesting topics have been chosen for discussion. As in previous years, there will be a continuous motion-picture program during the two days of general sessions. The scientific and

technical exhibits will be extensive and comprehensive and promise, more than ever, to be of great educational value.

Transportation difficulties have necessitated a curtailment of the ladies' program. No out-of-town trip could be scheduled, but there will be a reception and tea at the Hotel Statler on Tuesday afternoon, May 26, followed by a dinner at The Copley-Plaza, and a luncheon at the Women's City Club, on Wednesday, May 27.

Since the Nation *is* at war, the program is not only timely but of extreme interest and value, and for being able to plan such a meeting, in spite of the difficulties engendered by war activities, the Committee of Arrangements deserves the sincere thanks of all members of the Massachusetts Medical Society, which can best be shown by a record-breaking attendance.

THE ELLA SACHS PLOTZ FOUNDATION

According to its eighteenth annual report, the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation awarded, during the past year, thirty-five grants for research in medicine and surgery and in related branches of science. Since its establishment, the foundation has supported four hundred and twenty-nine projects in the United States and thirty-seven other countries. The maximum sum given to any single experiment or study has usually been less than five hundred dollars.

Although the original intention of the foundation, as expressed by the trustees, was to assist research on single problems in stipulated fields, the policy in recent years has been to encourage investigations in the sciences closely related to medicine, without reference to special fields. Thus, the fund now supports experiments varying in scope and purpose from research on typhus and different serologic types of hemolytic streptococci to work in endocrinology and chemical embryology and studies on the physiologic effects of high altitudes.

Of particular interest to physicians in Massachusetts are the awards that were made to Dr. George Barkan, of Boston University School of Medicine; Dr. Austin M. Brues, of the Huntington Memorial Hospital; Dr. R. W. Hickman, of the Cruft Laboratory, Harvard University; Dr. Otto Krayer, of the Harvard Medical School; Dr. Fritz Lipman, of the Massachusetts General Hospital; and the Thorndike Memorial Laboratory, Boston City Hospital. The last-named gift was in recognition of Dr. Francis W. Peabody's services to the foundation.

The dramatic events of a world engaged in total war naturally occupy our minds and obscure, but do not obliterate, the accomplishments made possible by such organizations as the Ella Sachs Plotz Foundation. We can win this struggle to preserve our national integrity and way of life only by striking with all our force against an enemy in whose philosophy there is no room for liberty, justice, decency and honor. With the victories, we must accept temporary retreats; we must learn to bear the thought of the inevitable slaughter and destruction. But the peace must also be won —and kept. The silent and untiring workers engaged in research fight an unending war in which they can never admit defeat—a struggle against the growths, the viruses, the deficiency diseases that plague mankind. It is these men who will show us how to keep and enjoy the benefits of the peace we are striving and praying for.

MEDICAL EPONYM

Osgood–Schlatter's Disease

Dr. Robert B. Osgood (b. 1873), of Boston, described "Lesions of the Tibial Tubercle Occurring During Adolescence" in the *Boston Medical and Surgical Journal* (**148**:114-117, 1903). The author made the following statements:

> The adolescent tibial tubercle, from its situation and mode of development, is susceptible to injuries, especially in athletic subjects. These lesions are usually caused by a violent contraction of the quadriceps extensor.
>
> Fracture and complete avulsions of the tubercle are rare, cause loss of function, and are easily diagnosed, usually clinically and always by means of the x-ray.

Avulsions of a small portion and partial separation of the tubercle are more common. They do not cause complete loss of function, but without treatment, long continued serious annoyance. The diagnosis should be made by a combination of the clinical and x-ray pictures, and before the latter are accepted as evidence both knees should be skiagraphed and accurate technique observed.

Professor Carl Schlatter (1864), of Zurich, independently discussed "Verletzungen des schnabelförmigen Fortsatzes der oberen Tibiaepiphyse [Injuries to the Beak-shaped Process of the Upper Epiphysis of the Tibia]" in Bruns's *Beiträge zur klinischen Chirurgie* (**38**:874-887, 1903). A portion of the translation follows:

There occurs, in the region of the knee, a typical form of injury, not very uncommon, whose clinical picture, in spite of all the recent advances in diagnosis, is not yet satisfactorily clear to us, as I realize from a fruitless search for a comprehensive study of this injury in the literature, and also from my own errors in diagnosis. This is the separation of the beak-shaped process of the upper tibial epiphysis, which encompasses the head of the tibia anteriorly.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

ANNUAL MEETING OF THE COUNCIL

The annual meeting of the Council will be held in the Georgian Room of the Hotel Statler, Boston, on Monday, May 25, 1942, at 7:00 p.m. This meeting will be preceded by the Cotting supper which will be served in Parlors A, B and C of the same hotel at 6:00 p.m.

Business:

1. Presentation of record of the special meeting of the Council held April 15, 1942, as published in the *New England Journal of Medicine*, issue of May 14, 1942.
2. Nominating Committee retires to deliberate.
3. Reports of standing and special committees.
4. Election of officers and orator.
5. Appointment of committees for ensuing year.
6. Such other business as may lawfully come before the meeting.

MICHAEL A. TIGHE, M.D., *Secretary*

COMMITTEE ON MATERNAL WELFARE

CASE HISTORY: RUPTURE IN TUBAL PREGNANCY, FOLLOWED BY DEATH

A thirty-eight-year-old housewife was seen at 10:00 a.m. by her physician. She had fainted three times and was reported to have abdominal colic with diarrhea. At 3:00 p.m. she was sent into the hospital in shock, practically pulseless, with no blood pressure, and died a few moments after admission. The past history was irrelevant. There had been one pregnancy twelve years previously, and the child was living and well. There was no history of skipped periods, although the hospital record was most inadequate. Autopsy revealed perforation of the right tube, and the abdomen was filled with blood clots.

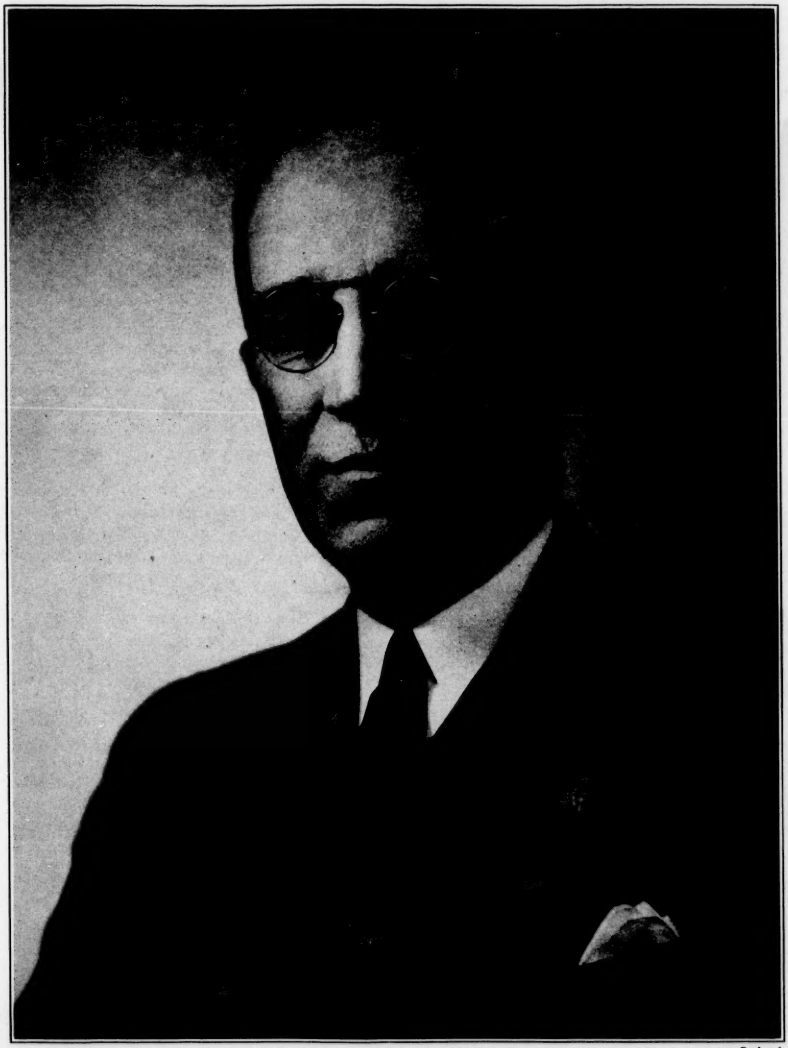
Comment. The inadequacy of the history is characteristic of many small hospitals in Massachusetts. The new law placing the licenses under the Massachusetts Department of Public Health will undoubtedly rectify this neglect. In all probability, if a history had been obtained and recorded, it would have stated some irregularity in the menstrual cycle immediately preceding this fatality. That five hours elapsed between the time when the patient was seen at home and her arrival at the hospital allows no interpretation except ignorance on the part of the physician who saw this patient, or utter lack of appreciation of the seriousness of her condition. Without doubt, because this patient fainted three times before she was seen by a physician, evidence of hemorrhage must have been present, had the practitioner been intelligent enough to observe it. There is, of course, no excuse for this lapse of five hours.

No specific diagnosis was made prior to death. The autopsy was performed by a medical examiner. The death certificate assigned the cause of death to internal hemorrhage, and the autopsy proved the death to have been puerperal in origin.

Whether this patient had been seen by a physician before the morning of her death is not disclosed in the record. If irregular bleeding, which certainly must have occurred, stimulated the patient to consult a physician and if medical advice was obtained, this fatality can surely be attributed solely to poor medicine. It illustrates the fact that ruptures in tubal pregnancies can bleed to the point of exsanguination, and that the only way to prevent a fatal outcome is to make the patient with irregular flowing in the early months of pregnancy understand that medical advice must be sought, and to make the physician realize that irregular flowing in the early months of pregnancy may mean a tubal pregnancy, the only intelligent treatment of which is hospitalization, vaginal examination and laparotomy, whenever there is a question of a pathologic pelvis.

MASSACHUSETTS MEDICAL SOCIETY

OFFICERS OF THE MASSACHUSETTS MEDICAL SOCIETY, 1941–1942



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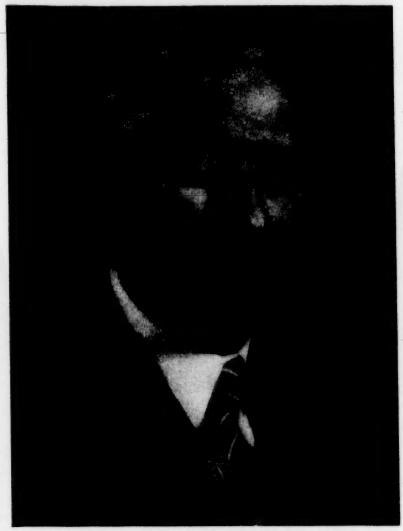
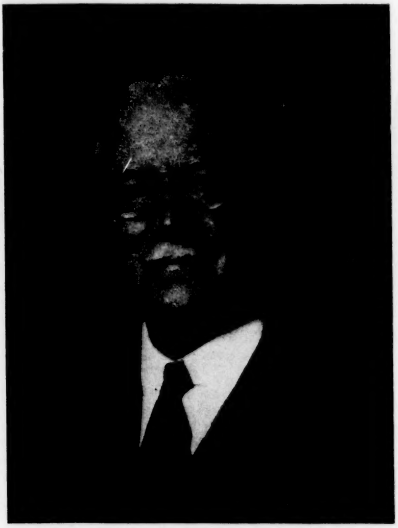
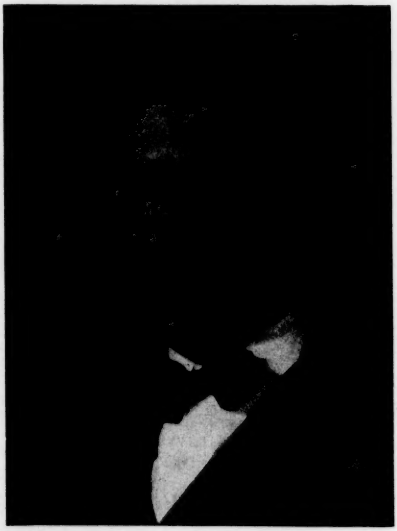
DR. GEORGE LEONARD SCHADT, *President-Elect*



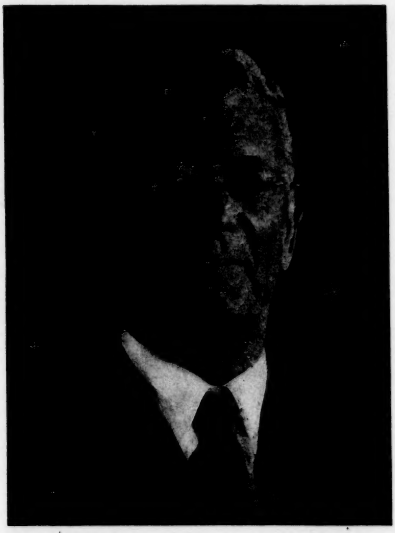
DR. FRANK R. OBER, *President*



DR. EDWARD P. BAGG, *Vice-President*



DR. MICHAEL A. TIGHE, *Secretary*



DR. CHARLES S. BUTLER, *Treasurer*

PROGRAM OF THE ONE HUNDRED AND SIXTY-FIRST ANNIVERSARY OF THE MASSACHUSETTS MEDICAL SOCIETY

Monday, Tuesday and Wednesday, May 25, 26 and 27, Hotel Statler, Boston

The exercises of the one hundred and sixty-first annual meeting of the Society will be held at the Hotel Statler, Boston, on Monday, Tuesday and Wednesday, May 25, 26 and 27. It should be noted that the program for the first day, Monday, May 25, provides no scientific session; the golf tournament at the Commonwealth Country Club is scheduled for the afternoon, and the annual meetings of the supervising censors and Council for the late afternoon and evening, respectively.

The Committee of Arrangements, which has planned the meeting, consists of Drs. William T. O'Halloran, chairman, James A. Halsted, George P. Sturgis, Henry H. Faxon and Gordon M. Morrison.

With the exception of some of the section meetings and luncheons, all activities will be located at the Hotel Statler. The scientific exhibits will fill the Ballroom Assembly, and the technical exhibits will occupy the Ballroom. On Tuesday and Wednesday, both in the morning and in the afternoon, motion pictures will be shown in the Lower Foyer.

The members' registration desk will be in the Ballroom, and that of the ladies on the Mezzanine Floor. All who attend are earnestly requested to register.

According to the arrangement a year ago, the annual dinner will be followed by the Shattuck Lecture, the dinner being scheduled to start at 7:00 p.m., Tuesday.

The luncheon meetings of the sections will be held Wednesday noon. Since it is necessary to have some idea of the number of members at these luncheons, all are urged to notify the committee at once if they plan to attend.

MONDAY EVENING, MAY 25

Annual Meeting of the Council of the Massachusetts Medical Society

5:00 **Supervising Censors' Meeting** (HANCOCK ROOM).

6:00 **Cotting Buffet Supper** (PARLORS A, B AND C).

7:00 **Council — Annual Meeting** (GEORGIAN ROOM).

Nominating Committee (HANCOCK ROOM).

TUESDAY MORNING, MAY 26

First General Session

GEORGIAN ROOM

Dr. Cadis Phipps, *Chairman*

Dr. Edward J. O'Brien, Jr., *Co-Chairman*

9:20 *Scarlet Fever Today.* Dr. Edwin H. Place: physician-in-chief, South Department, Boston City Hospital; clinical professor of pediatrics, Tufts College Medical School.

9:40 *The Problem of Certain Tropical Diseases in the War.* Dr. Henry E. Meleney (New York City): Hermann M. Biggs Professor of Preventive Medicine, New York University College of Medicine.

10:00 *Trauma of the Skin Due to Wartime Activities.* Dr. John G. Downing: assistant professor of dermatology, Tufts College Medical School; dermatologist, Boston City Hospital and St. Elizabeth's Hospital.

10:20 *Massachusetts Public-Health Problems in Wartime.* Dr. Paul J. Jakmauh: Commissioner, Massachusetts Department of Public Health.

10:40 *The Impact of the War on the Venereal-Disease Problem.* Dr. Raymond A. Vonderlehr (Washington, D. C.): Assistant Surgeon General, Division of Venereal Diseases, United States Public Health Service.

11:00 **Annual Meeting of the Massachusetts Medical Society.**

GEORGIAN ROOM

Annual Oration (following business meeting): *Some Remarks on Therapy for Anemia.* Dr. William B. Castle: professor of medicine, Harvard Medical School; associate director, Thorndike Memorial Laboratory; director, Second and Fourth Medical Services, Boston City Hospital.

Annual Luncheon (PARLORS A, B AND C): tickets may be procured at the Registration Desk.

TUESDAY AFTERNOON, MAY 26

Second General Session

GEORGIAN ROOM

Dr. George Leonard Schadt, *Chairman*

Dr. Ralph R. Stratton, *Co-Chairman*

2:00 *Hospital Preparedness.* Dr. Charles F. Wilinsky: executive director, Beth Israel Hospital; chief of Emergency Medical Services for Suffolk County.

2:20 *Medical-School Plans for the Emergency.* Dr. Bennett F. Avery: dean, Boston University School of Medicine; Waterhouse Professor of Anatomy, Boston University School of Medicine.

2:40 *The Doctor's Role in First Aid.* Dr. A. William Reggio: visiting surgeon, Massachusetts General Hospital; deputy director, Medical Division, Massachusetts Committee on Public Safety.

3:00 *Civilian Medical Defense in Massachusetts.* Dr. Elliott C. Cutler: Moseley Professor of Surgery, Harvard Medical School; surgeon-in-chief, Peter Bent Brigham Hospital; director, Medical Division, Massachusetts Committee on Public Safety.

3:20 *American Medicine and the War.* Dr. Morris Fishbein (Chicago): editor, *Journal of the American Medical Association.*

3:40 *Is Tuberculosis Increasing?* Dr. John A. Foley: professor of medicine, Boston University School of Medicine; chief-of-staff, Boston Sanatorium; director, Fifth and Sixth Medical Services, Boston City Hospital.

4:00 *The Interrelationship of Anesthesia with Analgesia.* Dr. Joseph F. McCarthy (New York City): director, Department of Urology, New York Polyclinic Medical School and Hospital.

4:20 *Hypertension: Present status of the problem.* Dr. Robert W. Wilkins: assistant professor of medicine, Boston University School of Medicine.

4:40 *The Present Program for the Immunization of Troops.* Dr. John F. Enders: assistant professor of bacteriology, Harvard Medical School.

TUESDAY EVENING, MAY 26

Annual Dinner of the Massachusetts Medical Society

SALLE MODERNE

7:00 p.m.

Guest Speakers:

Dr. Frank H. Lahey: president, American Medical Association.

Dr. Morris Fishbein (Chicago): editor, *Journal of the American Medical Association.*

The Shattuck Lecture (GEORGIAN ROOM) (following annual dinner). *Medicine and Air Supremacy.* Dr. John F. Fulton (New Haven, Connecticut): Sterling Professor of Physiology, Yale University School of Medicine.

WEDNESDAY MORNING, MAY 27

Third General Session

GEORGIAN ROOM

Dr. A. A. Hornor, *Chairman*

Dr. Edward P. Bagg, *Co-Chairman*

9:00 *Carcinoma of the Bronchus.* Dr. George W. Holmes: professor of clinical roentgenology, emeritus, Harvard Medical School; consulting roentgenologist, Massachusetts General Hospital.

9:20 *Clinical Application of Gastroscopy.* Dr. Charles W. McClure: junior visiting physician and gastroscopist, Fifth Medical Service, Boston City Hospital; and Dr. I. R. Jankelson: assistant professor of medicine, Tufts College Medical School; junior visiting physician, Boston City Hospital.

9:40 *The Procurement and Assignment of Physicians during the Present Emergency.* Dr. Reginald Fitz: Massachusetts State Chairman, Procurement and Assignment Service, Office of Defense, Health and Welfare Services.

10:00 *The Relation of Medicine to the Emergency.* Dr. Frank H. Lahey: president, American Medical Association; chairman, Procurement and Assignment Service; director of surgery, Lahey Clinic; surgeon-in-chief, New England Deaconess Hospital and New England Baptist Hospital.

10:20 *Management of the Acute Stage of Infantile Paralysis.* Dr. Frank R. Ober: John B. and Buckminster Brown Clinical Professor of Orthopaedic Surgery, Harvard Medical School; chief of Orthopedic Department, Children's Hospital; orthopedic surgeon, Peter Bent Brigham Hospital; chief surgeon, New England Peabody Home for Crippled Children.

10:40 *Typhus Fever.* Dr. R. E. Dyer (Bethesda, Maryland): director, National Institute of Health, United States Public Health Service.

11:00 *Industrial Health in National Defense.* Dr. Daniel L. Lynch: medical director, New England Telephone and Telegraph Company.

11:20 *A Further Report on Para-Aminobenzoic Acid and Its Relation to Gray Hair.* Dr. Benjamin F. Sieve: instructor in medicine, Tufts College Medical School; junior visiting physician, Boston City Hospital.

11:40 *World Conflict and Medical Service.* Mr. John M. Pratt (Chicago): executive administrator, National Physicians' Committee for the Extension of Medical Services.

WEDNESDAY NOON, MAY 27

Section Meetings and Luncheons

12:00 m.–2:00 p.m.

Sections of Medicine and Surgery

PARLORS A, B AND C

Dr. Erwin C. Miller, Worcester, *Chairman — Medicine*

Dr. Charles L. Short, Boston, *Secretary — Medicine*

Dr. Grantley W. Taylor, Boston, *Chairman — Surgery*

Dr. James C. McCann, Worcester, *Secretary — Surgery*

The Vascular Dynamics, Recognition and Management of Shock. Dr. Virgil H. Moon (Philadelphia): professor of clinical pathology, Jefferson Medical College of Philadelphia.

Section of Pediatrics

THE JUNIOR LEAGUE, ZERO MARLBOROUGH STREET

Dr. Philip H. Sylvester, Boston, *Chairman*

Dr. James Marvin Baty, Brookline, *Secretary*

The Common Cold. Dr. Francis L. Weille: associate surgeon, Massachusetts Eye and Ear Infirmary; assistant in otolaryngology, Harvard Medical School.

Section of Obstetrics and Gynecology

THE TAVERN CLUB, 4 BOYLSTON PLACE

Dr. M. Fletcher Eades, Boston, *Chairman*
Dr. Raymond S. Titus, Boston, *Secretary*

Vaginal Discharge. Dr. John Rock: visiting surgeon, Free Hospital for Women; instructor in gynecology and research associate in obstetrics, Harvard Medical School.

Section of Radiology and Physiotherapy

PARLORS D AND E

Dr. Joseph H. Marks, Boston, *Chairman*
Dr. Henry A. Tadgell, Wrentham, *Secretary*

Symposium on Bronchial Obstructions.

Dr. Edward B. Benedict: assistant in surgery, Harvard Medical School; associate visiting surgeon, Massachusetts General Hospital.

Dr. Richard H. Overholt: thoracic surgical consultant, New England Deaconess Hospital and Corey Hill Hospital; surgeon-in-chief, Thoracic Clinic, Boston Dispensary.

Dr. Merrill C. Sosman: clinical professor of roentgenology, Harvard Medical School; roentgenologist-in-chief, Peter Bent Brigham Hospital.

Section of Dermatology and Syphilology

PARLOR F AND THE HANCOCK ROOM

Dr. Arthur M. Greenwood, Boston, *Chairman*
Dr. William J. Macdonald, Boston, *Secretary*

Eczema and Pruritus in the Aged. Dr. Leonard E. Anderson: dermatologist, Out-Patient Department, Springfield Hospital; dermatologist, Wesson Memorial Hospital, Springfield.

WEDNESDAY AFTERNOON, MAY 27

Fourth General Session

GEORGIAN ROOM

Dr. Donald Munro, *Chairman*
Dr. Frederick J. Lynch, *Co-Chairman*

2:00 *The Early Treatment of Burns.* Dr. Donald W. MacCollum: associate in surgery, Harvard Medical School; associate in plastic surgery, Peter Bent Brigham Hospital; associate visiting surgeon, Children's Hospital.

2:20 *The Five-Year Report on Cesarean Section in Massachusetts (1937–1941).* Dr. Robert L. DeNormandie: member, State and Federal Advisory Committees on Maternal and Child Hygiene.

2:40 *The Choice of Drug in the Treatment of Infections.* Dr. Charles H. Rammelkamp: instructor in medicine, Boston University School of Medicine.

3:00 *Deficiency Diseases of the Oral Cavity.* Dr. David Weisberger: instructor in oral medicine, Harvard Dental School.

3:20 *The Sequela of War Head Injuries.* Dr. Derek Denny-Brown: professor of neurology, Harvard Medical School.

3:40 *War Dermatology.* Dr. C. Guy Lane: clinical professor of dermatology, Harvard Medical School; chief of Department of Dermatology, Massachusetts General Hospital.

4:00 *Symposium on Minor Psychiatric Disturbances in War and Civilian Life.*

The Diagnosis of Psychoneurotic Disturbances. Dr. Donald J. MacPherson: associate in medicine, Peter Bent Brigham Hospital.

The Psychiatric Approach in Medicine: Psychosomatic medicine. Dr. Jacob E. Finesinger: assistant professor of psychiatry, Harvard Medical School; psychiatrist, Massachusetts General Hospital.

Therapy in the Psychoneuroses. Dr. Erich Lindemann: associate in psychiatry, Harvard Medical School; associate psychiatrist, Massachusetts General Hospital.

Motion Picture Program

LOWER FOYER

Tuesday, May 26

9:30–10:30 *Prevention and Treatment of Eclampsia.*
10:30–10:45 *Diagnostic Procedures in Tuberculosis.*
10:45–11:00 *Emergency Treatment for Fractures.*
11:00–11:30 *Technique of Blood Transfusions.*
11:30–12:00 *Treatment of Asphyxia Neonatorum.*
2:00– 2:45 *Diagnosis and Treatment of Infections of the Hand.*
2:45– 3:15 *First Aid in Transporting Fractures of the Leg, Spine and Arm.*
3:15– 3:30 *Protruded Intervertebral Disk: Diagnosis and surgical treatment.*
3:30– 4:00 *Cardiac Irregularities.*
4:00– 4:15 *Splenectomy.*
4:15– 4:30 *The Use of Extra Fine Catgut.*

Wednesday, May 27

9:30–10:30 *Sex Hormones, Physiology, Diagnosis and Therapy.*
10:30–11:00 *Vaginal Hysterectomy: Suture method.*
11:00–11:15 *Vaginal Hysterectomy: Clamp method.*
11:15–11:45 *Treatment of Burns.*
2:00– 2:15 *Transverse Cervical Cesarean Section.*
2:15– 2:30 *Hernioplasty.*
2:30– 3:15 *Physiology and Conduct of Normal Labor.*
3:15– 3:45 *Acute Appendicitis.*
3:45– 4:30 *Arteriosclerotic Heart Disease.*

Scientific Exhibits

BALLROOM ASSEMBLY

Booth

S-10 *The Pathology of Skin Tumors.* Massachusetts State Tumor Diagnostic Service. Exhibitors: Dr. Shields Warren and Dr. Olive Gates.

S-15–16 *First Aid in Fractures.* Massachusetts Committee on Fractures and Trauma, American College of Surgeons; Medical Division, Massachusetts Committee on Public Safety; Boston Metropolitan Chapter, American Red Cross.

S-17 *Study and Treatment of Alcoholism.* The Washingtonian Hospital. Exhibitor: Dr. Merrill Moore, director of research.

S-18 *The Senescent Skin and Its Diseases.* Dr. C. Guy Lane, Dr. Arthur M. Greenwood and Dr. Ethel M. Rockwood.

S-19 *Blood for Victory.* Blood Donor Center, Boston Metropolitan Chapter, American Red Cross. Exhibitor: Mr. Wesley Fuller, director.

S-20 *Sigmoidoscopy.* The Gastrointestinal Clinic, Boston City Hospital. Exhibitors: Dr. Charles W. McClure and Dr. I. R. Jankelson.

S-21 *Intercapillary, Glomerulosclerosis.* Fifth and Sixth Medical Services, Boston City Hospital; Boston University School of Medicine; Mallory Institute of Pathology, Boston City Hospital. Exhibitors: Dr. Harold Jeghers and Dr. Oscar Wollenman.

S-22–24 *Biliary Tract Disease.* Evans Memorial Hospital, Massachusetts Memorial Hospitals, Boston.

1. *Gallstones: Composition and etiology.* Dr. Knowles B. Lawrence.
2. *Roentgenologic Study of the Gallbladder.* Dr. George Levene.
3. *Pathology of Acute Cholecystitis.* Dr. Charles F. Branch.
4. *Surgical Treatment of Acute Cholecystitis.* Dr. Howard M. Clute.
5. *Duodenal Drainage.* Dr. Franz J. Ingelfinger.
6. *Strictures of the Common Duct.* Dr. Howard M. Clute.
7. *Gallstone Ileus.* Dr. Egon G. Wissing and Dr. Knowles B. Lawrence.
8. *Preoperative and Postoperative Care in Obstructive Jaundice.* Dr. Thomas J. Anglem.

S-25–26 *Anesthesia.* Massachusetts members of the New England Society of Anesthesiology.

S-27 *Fractures.* The Faulkner Hospital. Exhibitors: Dr. Gordon MacK. Morrison and Dr. Harvey R. Morrison.

S-28–29 *New Standards of Efficiency of Treatment in Diabetes Mellitus.* Dr. Elliott P. Joslin and associates.

S-30–31 *Skeletal Traction and Countertraction Methods Applicable to Ordinary Extension Splints Used in the Treatment of the Fractures of the Lower Extremity. Rupture of Biceps Brachii.* United States Marine Hospital, Boston. Exhibitor: Dr. Richey L. Waugh.

S-32–33 *Surgical Pathology.* The Fallon Clinic, Worcester. Exhibitors: Dr. John Fallon, Dr. James T. Brosnan and Dr. William G. Moran.

S-34 *Occupational Therapy.* Massachusetts Association for Occupational Therapy.

CORRIDOR

A *Diseases of the Biliary Tract.* The Lahey Clinic. Exhibitors: Department of Surgery.

B *Nutrition.* Massachusetts Department of Public Health.

Technical Exhibits

BALLROOM

	BOOTH NO.
Abbott Laboratories	22
Alkalol Company	14
American Hospital Supply Corporation	40
Artra Cosmetics, Inc.	49
The Baker Laboratories	39
Bilhuber–Knoll Corporation	41
Ernst Bischoff Company, Inc.	24
The Borden Company	20
Brewer and Company	9 and 10
Burroughs Wellcome & Co. (U. S. A.), Inc.	31
Cambridge Instrument Company, Inc.	4
Camel Cigarettes	15 and 16
Campbell X-Ray Corporation	46
Certified Milk Producers Association	S-1
Ciba Pharmaceutical Products, Inc.	S-5
Crosbie–Macdonald	13
Davies, Rose & Company, Ltd.	47
Mrs. Day's Ideal Baby Shoe Co.	2
Devereux Schools	S-3
The Doho Chemical Corporation	56
Dy-Dee Service, Children Incorporated	12
J. H. Emerson Company	S-13
C. B. Fleet Co., Inc.	51
General Electric X-Ray Corporation	26
Gerber Products Company	29
J. E. Hanger, Inc.	61
Hanovia Chemical and Manufacturing Company	8
H. J. Heinz Company	7
Horlick's Malted Milk Corporation	S-4
"The 'Junket' Folks"	36
Kellogg Company	S-6
Lederle Laboratories, Inc.	45
Lee DeForest Laboratories	28
Liebel–Flarsheim Company	32
Eli Lilly and Company	50
M. & R. Dietetic Laboratories, Inc.	25
E. F. Mahady Company	37 and 38
Massachusetts Hospital Service, Inc. (Blue Cross)	6
Massachusetts State Pharmaceutical Association	43
Mead Johnson & Company	58 and 59
The Medical Protective Company	30
Mellin's Food Company of North America	35
The Mennen Company	34
T. J. Noonan Company	S-12
Parke, Davis & Company	S-2
The E. L. Patch Company	23
Pet Milk Sales Corporation	S-7
Petrogalar Laboratories, Inc.	1
Philip Morris & Co., Ltd., Inc.	52
Picker X-Ray Corporation	19
Randall Faichney Corporation	S-9
Thomas W. Reed Company	S-14
Riedel-de Haen, Inc.	S-11
S. M. A. Corporation	5
Sanborn Company	21
Sandoz Chemical Works, Inc.	44

Schering Corporation 48
G. D. Searle & Company S-8
Sharp & Dohme, Inc. 55
Smith, Kline & French Laboratories 53
E. R. Squibb & Sons 33
Standard X-Ray Sales Corporation 11
The Sun-Rayed Company 17
Surgeons' and Physicians' Supply Company 60
Tailby–Nason Company 27
Trixie Corporation 3
White Laboratories, Inc. 42
Winthrop Chemical Company, Inc. 54
John Wyeth & Brother, Inc. 57

LADIES' PROGRAM

Mrs. Frank R. Ober, *General Chairman*

Tuesday, May 26

Registration. 9:00 a.m.–5:00 p.m.
MEZZANINE FLOOR, HOTEL STATLER

Reception and Tea. 3:30 p.m.
SALLE MODERNE, HOTEL STATLER

Dinner. 7:30 p.m.
THE COPLEY-PLAZA
Tickets on sale at Registration Desk

Wednesday, May 27

Registration. 9:00 a.m.–12:00 m.
MEZZANINE FLOOR, HOTEL STATLER

Luncheon. 1:00 p.m.
WOMEN'S CITY CLUB OF BOSTON, 40 BEACON STREET
Tickets on sale at Registration Desk

ANNUAL GOLF TOURNAMENT

The annual golf tournament of the Massachusetts Medical Society will be held at the Commonwealth Country Club, 91 Algonquin Road, Chestnut Hill (Newton), on Monday, May 25. The Burrage Bowl, the Society's championship trophy for the lowest net score, and other prizes for both net and gross play should stimulate interest in this tournament. Play will begin at 1:00 p.m. The greens fee for 18 holes is $2.00; for two or more rounds, $2.50. For additional information, communicate with Mr. Robert St. B. Boyd, executive secretary, 8 Fenway, Boston (KEN 2094), or a member of the Golf Committee, which is composed of the following: Dr. Roy J. Heffernan, Chairman, Dr. Edward A. Cooney, Dr. Thomas E. Dinan, Dr. Allan L. Davis and Dr. Roger T. Doyle.

COMMITTEE ON POSTGRADUATE INSTRUCTION

A luncheon meeting of the district chairmen of the Committee on Postgraduate Instruction will be held on the fourth floor of the Hotel Statler on Wednesday, May 27, at 12:30 p.m. (Inquire at information desk for the room number.)

MASSACHUSETTS MEDICO-LEGAL SOCIETY

A meeting of the Massachusetts Medico-Legal Society will be held on the fourth floor of the Hotel Statler on Tuesday, May 26, at 2 p.m. (Inquire at information desk for the room number.)

DEATHS

BALDAUF — LEON K. BALDAUF, M.D., of Waltham, died April 30. He was in his sixty-fifth year.

Dr. Baldauf received his degree from Johns Hopkins University School of Medicine in 1905. He became a member of the faculty of Albany Medical College and later served as professor of pathology and bacteriology at University of Louisville School of Medicine. He had recently been appointed professor of pathology at Middlesex University School of Medicine. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow survives him.

BARNES — FRANCIS J. BARNES, M.D., of Cambridge, died April 28. He was in his eightieth year.

Born in Newton, Dr. Barnes received his degree from Harvard Medical School in 1888. From 1916 to 1926 he was chief of staff of the Cambridge City Hospital. He was a member of the Massachusetts Society of Examining Physicians, and was a fellow of the Boston Medical Library, the Massachusetts Medical Society and the American Medical Association.

He is survived by his widow, a daughter and two grandchildren.

BENSON — CHARLES S. BENSON, M.D., of Haverhill, died April 30. He was in his seventieth year.

Born in Lewiston, Maine, Dr. Benson received his degree from Columbia University College of Physicians and Surgeons in 1896. He had practiced surgery in Essex County for many years and was the head of the Benson Hospital. Dr. Benson was vice-chairman of the medical advisory board of District No. 4, Selective Service System, and had served as a draft-board physician during World War I. He was a former president of the Essex North District Medical Society, and was a fellow of the American College of Surgeons, the Massachusetts Medical Society and the American Medical Association.

CELCE — FRANK F. CELCE, M.D., of Holyoke, died April 28. He was in his seventy-fifth year.

A native of Germany, Dr. Celce received his degree from University of Pennsylvania School of Medicine in 1893. He was a member of the Massachusetts Medical Society and the American Medical Association.

A son and a daughter survive him.

DAMON — ARTHUR L. DAMON, M.D., of North Wilbraham, died April 30. He was in his seventy-fifth year.

Born in West Cummington, Dr. Damon received his degree from University of Vermont College of Medicine in 1890. He was a fellow of the Massachusetts Medical Society and the American Medical Association.

His widow, a brother and a sister survive him.

DURGIN — EDWARD C. DURGIN, M.D., of Marshfield, died April 26. He was in his sixty-fifth year.

Dr. Durgin received his degree from Tufts College Medical School in 1901. He was a former member of the Massachusetts Medical Society and the American Medical Association.

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